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THE MONTH

The Symposium

'No current theory of the etiology of rheumatoid arthritis rests on really firm foundations' and it is 'impossible on the basis of recent theories of etiology to suggest any alternative to our present empirical approach to treatment'. It is on this realistic, if somewhat depressing, note that Dr. A. G. S. Hill begins and ends his introductory article in our symposium on 'The Problem of Rheumatism' this month. Pending the unravelling of this Gordian knot, it is incumbent upon the practitioner to be able to do everything possible to ameliorate the lot of his rheumatic patients. It is upon this aspect of the subject that stress is laid in the symposium. The victim of chronic rheumatism—as of any other chronic condition—is particularly susceptible to the extravagant claims made for unorthodox forms of treatment, and it is not unnatural that on occasion the harrassed practitioner should lose patience with those of his rheumatic patients who demand such treatment from him. What the wise doctor soon realizes, however, is that the secret of success in the management of these unfortunate people is an understanding of them as individuals. The confidence of the patient in his doctor is the basis of all sound therapy, always provided that the doctor can guarantee the best possible treatment available at the moment.

The First Decade

It is with mixed feelings that the medical profession looks back upon the first ten years of the National Health Service: relief that it has proved as successful as it has; disappointment that on so many occasions principles have been sacrificed to expediency. The debit side of the balance sheet makes despondent reading: doctors inundated with paper work, compelled to take more patients than they want to, submitted to repeated petty persecutions, virtually denied freedom of movement, and segregated into watertight compartments. It is scarcely surprising that in these circumstances the profession is frustrated and despondent. On the credit side is the fact, of which the nation has reason to be proud, that every citizen of these Islands, irrespective of his financial status, has been able to benefit from the dramatic advances of these last ten years.

Not unnaturally—indeed rightly—the responsibility for many of the defects of the Service must rest fairly and squarely upon the shoulders of the Governments who have been in power since the Service was introduced, but it is essential to maintain a sense of proportion. The faults have not all been on one side. Too many patients have looked upon the Service as a universal provider of expensive medicine and of certificates for exemption

from duties which they wish to shirk. Doctors, too, have been at fault and too many have abused the degree of freedom—generous by Civil Service standards—which they were allowed. Perhaps most disturbing of all from the point of view of the profession has been the lack of constructive suggestions from its official representatives. Why, if the Service is as heinous as so many make it out to be, has it been left to the Fellowship for Freedom in Medicine to produce the only alternative scheme? Why has not the British Medical Association produced a constructive plan for modifying the Service so as to make it more compatible with the traditional standards of the healing art? The Service undoubtedly requires reform. The tragedy of these last ten years is that the country has looked in vain to the medical profession for the means whereby such reform could best be carried out.

The Second Decade

THIS, then, is the challenge to the profession as we stand on the threshold of the new decade. In considering reform, however, two points must never be forgotten. The first is that, for better or for worse, the National Health Service has come to stay. The second is the changing social climate of the age. The concept of the Welfare State has also come to stay. To oppose it is futile. To guide it along the right lines is statesmanship. It is not incompatible with the traditional concept that there are no rights without duties, and the duty of the Government, and of the profession, is to ensure that this concept be carried into practice so far as the National Health Service is concerned.

On the part of the Government this means that they must use every modern method of propaganda to persuade the people to use and not abuse the Service. They must restore the general practitioner to his rightful place as the family doctor, give him those facilities which will allow him to do justice to his patients, and ensure an adequate remuneration which is based upon the quality rather than the quantity of work. They must give private patients the same access to drugs under the Service as they would have if they accepted the full facilities to which they are entitled. They must relieve regional hospital boards of the many unnecessarily restrictive measures imposed upon them. The profession, on its side, must take more active steps to deal with that minority of doctors who are abusing the freedom they are granted under the Service. Too many doctors are prescribing too many expensive drugs. There is an insidious tendency for doctors to consider that cost is of no significance if the bill is paid by the State, forgetting that the cost is just as important today as it was in the days of private practice. No patient must be deprived of the benefit of a drug simply on the grounds of expense but, at the same time, an expensive drug should not be prescribed if there is an equally effective one which costs less. Equally important is the problem of the assistant in general practice. How much of the present discontent among assistants is due to the lack of understanding of their needs on the part of principals? Finally, immediate steps should be taken to deal with those practitioners who are deliberately retaining the maximum number

of patients and then acting merely as clerks—referring every patient who requires careful attention to hospital.

Who Pays?

It is now practically forty years since, in his presidential address to the Labour Party, Sidney Webb introduced into popular parlance his concept of the 'inevitability of gradualness'. The intervening years have amply confirmed the validity of his thesis. Indeed, so gradual has been the penetration of State control into our private lives that it is difficult at times to appreciate the extent to which practically every citizen is now dependent upon Exchequer subventions. In many instances these subventions are well publicized, and correspondingly well known—housing subsidies, free education, free school meals. What is not so well appreciated is the extent to which other activities are subsidized by the State. Perhaps the best example of this is the case of university fees. Sir Edward Appleton, the Principal of Edinburgh University, has recently drawn attention to the fact that students' fees represent only 10.6 per cent. of the income of the university, compared with over 22 per cent. in 1939. Parliamentary and other grants now represent practically 80 per cent. of the university's income. In other words, as Sir Edward Appleton points out, 'even a student who is able to pay his own fees is educated largely at the public expense'.

The implications of this state of affairs seem to be among the blind spots of many who ought to know better. At one time it could be argued that the long and expensive training required for entrance to the medical profession justified a correspondingly high remuneration once the student embarked upon his professional career. What justification is there now for such a claim when the Exchequer subsidizes his university training to the extent of 80 per cent., even though he gets no allowance from his local authority? Is it possible that the day may come when the Soviet policy may be adopted, and a newly qualified doctor will be expected—in return for his education—to serve for a period in a 'directed' post? Have all those educational, scientific and professional organizations who are crying out for government subsidies forgotten the old adage that he who pays the piper calls the tune. Hitherto, successive Governments have resisted the attempts of Parliament to interfere with the freedom of the universities to spend their Exchequer grants as they considered best, but the demands for such interference are becoming increasingly insistent. We in the medical profession are particularly vulnerable. The 'inevitability of gradualness' may be a disturbing phenomenon in the form of the modern Welfare State, but it is one which must be faced.

Spiritual Healing

It is a sign of the times that, almost simultaneously, both the Church of England and the Church of Scotland should have published reports on spiritual healing. Taken in conjunction with the comparable report published by the British Medical Association two years ago, these two reports present an authoritative review of the subject which will commend itself to all thoughtful practitioners. Time was—and not so very long ago—when Church and Medicine held

each other at arm's length. A wave of materialism swept over Medicine as it exulted in the power placed in its hand by the scientific advances of the latter part of the 19th century, and in its arrogance it assumed that it could do all things unaided. The Church, for its part, smarting from the attacks of the Tractarians on the one side and of the ultra-Darwinists on the other, withdrew within its theological shell and left the healing of the sick, in the conventional sense, to the medical profession.

Today the position is completely changed. As the Archbishops' commission ('The Church's Ministry of Healing'. The Church Information Board, price 2*s.* 6*d.*) points out, 'this traditional separation is now widely felt to have outlasted its usefulness and is under fire from all directions, whether scientific or metaphysical'. The patient is no longer regarded as an interesting case of this, that or the other. Medicine, to quote the report of the Archbishops' commission again, 'is laying increased emphasis on the unity of man's nature, recognizing more and more that the causes of much physical illness and mental disturbances are to be found in the deep and intimate relationship of the physical, mental, moral and spiritual in man'. In the widespread acceptance of this holistic outlook in medicine lies the greatest hope of arresting the current wave of 'psychosomatic' disease that is sweeping over western civilization. Doctor and priest are indeed complementary in the healing art. Now that both Church and Medicine have shown that they accept this fact, it is for the rank and file of each to ensure that the sick citizen has the full benefit of their active cooperation.

On Becoming A Nonagenarian

WITH this issue *The Practitioner* enters the ranks of the nonagenarians. Little did its founders envisage the world—medical, scientific, or social—in which their successors today would be working. The modern welfare state with its encircling sputniks, in which surgeons daily widen stenosed mitral valves in hospitals equipped with radioactive units, would indeed have seemed a strange place to them. On the fundamentals of life and medical practice, however, we would still understand each other: the family doctor as the guardian of the people's health, the importance of the doctor-patient relationship, and the tradition of service as the keynote of the profession. Equally would we understand each other on the purpose of *The Practitioner:* to provide the practitioner—whether in general or consulting practice—and in whatever part of the world he may live—with a continuing postgraduate course covering the whole field of clinical practice. We appreciate the steady stream of appreciative letters which we receive from readers at home and abroad. Equally do we appreciate the many suggestions we receive for subjects to be dealt with in our pages. As we enter this last lap before our century we assure our readers that it will be our continuing aim to guide them through the maze of advancing medicine, helping them to sort the grain from the chaff, and so aid them in bringing the best of medical knowledge to the patients entrusted to their care.

ETIOLOGY OF RHEUMATOID ARTHRITIS

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No current theory of the etiology of rheumatoid arthritis rests on really firm foundations and it is not easy to predict which type of basic research or clinical investigation is most likely to make the next major leap forward and thereby point the way for concerted effort. It is therefore legitimate to search for clues throughout the whole broadening field of knowledge about the clinical, biochemical, histological and serological manifestations of the disease. I have accordingly thought it best in this account to survey the sources of information which may guide us towards a theory before assembling some of the evidence which favours individual hypotheses.

CLINICAL INVESTIGATION AND POPULATION STUDIES

The validity of statistics based on the clinical observation of patients with rheumatoid arthritis seen at hospital clinics or in general practice is lessened by the knowledge that many victims of the disease never seek medical help. Dependable information about the true incidence, the frequency in each sex, the age at onset and other things can come only from field studies of the general population. If the incidence varies from country to country, or in different parts of one country, such variations can be established only if standard methods are used for diagnosing the disease. Such methods, based on clinical, radiographic and serological criteria have recently been developed and some of the fruits of this type of investigation will be discussed later. The most detailed statistically controlled analyses of the disease as it is seen in hospital have been made in this country by the Empire Rheumatism Council (1950), and in the United States by Short, Bauer and Reynolds (1957).

CONNECTIVE TISSUE STUDIES

Developmentally a joint is a cleft formed in mesoderm as a response to a demand for free movement at a certain point. Articular cartilage and, of course, the bone it covers, are developed in the same tissue in response to a different functional need. Hence the tissues involved in any form of arthritis are mesodermal in origin. Rheumatoid arthritis is fundamentally a disease of connective tissue, and lesions in sites other than joints are well recognized. Studies of connective tissue—its histochemistry, metabolism and the ways in which it can respond to damage—are therefore appropriate approaches to the problem of the pathogenesis of rheumatoid arthritis. Apart from its

cellular constituents, connective tissue is composed of fibrous elements (collagen, reticulin, elastin) and amorphous ground substance. Studies of collagen, by chemical analysis, electron microscopy and x-ray diffraction, and of the chemistry of ground substance (notably hyaluronic acid and chondroitin sulphate) have produced a mass of data which cannot be fully considered in the short compass of this survey.

In my department we have been concerned with studying the elements of connective tissue which will stimulate the formation of antibodies when injected into an animal of a different species. Antibodies are readily produced which will react with basement membranes and reticulin (Hill and Cruickshank, 1953; Cruickshank and Hill, 1953). Basement membranes are generally regarded as condensations of ground substance and reticulin as a precursor of mature collagen. Scott (1957) has recently established that the reticulin and basement membrane antigens are distinct from each other. The former is well represented in synovial tissue and neither can be identified with any of the extractable components of connective tissue. The reticulin antigen may be the same polysaccharide which is responsible for argyrophilia and which is absent from mature collagen. Collagen itself is only weakly antigenic.

SEROLOGICAL PHENOMENA

Serological phenomena are at present one of the major growing points of knowledge about rheumatoid arthritis and the subject of intensive research. A comprehensive review has been published recently (Ziff, 1957). Interest in this field springs largely from the rediscovery by Rose *et al.* (1948) of a phenomenon originally described by Waaler (1940) who noticed in the course of complement fixation tests, that his 'sensitized' sheep erythrocytes were agglutinated by serum from cases of rheumatoid arthritis. Sensitization of the red cells in this context is accomplished by coating them with a layer of antibody produced in response to injections of sheep erythrocytes into an animal of a different species, usually rabbit. In the test a concentration of antibody is selected which is just too low to agglutinate the cells which it coats. In effect these prepared cells can be regarded as having on their surface a layer of rabbit gamma globulin: their agglutination by rheumatoid arthritis serum seems to indicate a reaction between this globulin and a factor in the serum. It is possible to replace rabbit immune globulin by normal human gamma globulin adsorbed on inert particles of latex or bentonite. Serum from cases of rheumatoid arthritis sometimes forms a precipitate spontaneously—probably as the result of a reaction between its gamma globulin and the 'rheumatoid factor'. The factor has therefore some of the attributes of an antibody to gamma globulin (human or animal); it seems to react most readily with globulin spread on the surface of a cell or particle or slightly denatured, as by heating. A similar or identical factor is probably responsible for the agglutination of streptococci by a proportion of speci-

mens of serum from rheumatoid arthritis. In this reaction the streptococcal cells are probably sensitized by a weak natural antibody and then agglutinated by the specific rheumatoid factor present in the same serum.

Patients with systemic lupus erythematosus often have a polyarthritis indistinguishable from that of rheumatoid arthritis. Furthermore, serum from a proportion of patients with rheumatoid arthritis will produce the lupus erythematosus cell phenomenon. There is therefore sufficient evidence of an overlap between these diseases to justify examination of the lupus erythematosus phenomenon as a possible clue to the etiology of rheumatoid arthritis. The genesis of lupus erythematosus cells starts with an interaction between the nucleoprotein of the substrate cells (which need not be of human origin) and a factor present in the patient's serum to which they are exposed. This factor behaves like an antibody to nucleoprotein and, like the rheumatoid factor, is not species-specific.

EXPERIMENTAL LESIONS

In its histological reaction to damage, however determined, the repertoire of mesenchymal tissue may be limited. Hence similarity of natural and of experimentally produced lesions is insecure evidence for identity of cause. The pathological picture of the disease in man can, perhaps, be most closely mimicked by two infective conditions in animals: one produced in rats by infection with pleuropneumonia-like organisms, the other in swine by *Erysipelothrix rhusiopathiæ*.

Lesions in joints can be readily produced by a local antigen-antibody reaction. Such a reaction can be staged by sensitizing an animal with serum from another species and then injecting some of the same foreign serum into a joint. This is a rather artificial situation and not easy to translate into terms of naturally occurring disease. Synovial tissue, however, is quite actively phagocytic and it is possible that foreign material segregated therein may cause damage—either directly or by forming the target for an antibody evoked by its presence in the body. There are other possibilities, and the field provides a happy hunting ground for speculation. The foreign material accumulated in the synovia might, for example, be a hapten, which forms a complete antigen only after combination with some component of connective tissue. It is possible to study the uptake of foreign antigens by the tissues with fluorescein-labelled antibodies, used as readily recognizable tracers. By this method a bacterial polysaccharide of large molecular size (from the capsule of the Friedländer bacillus, type B) was found to be taken up in quite large amounts by the synovial tissue of small rodents into which it had been injected intravenously or intraperitoneally. The polysaccharide remains in this and other sites for several weeks (Hill, Deane and Coons, 1950). The same polysaccharide produces a form of synovitis which appears to be due neither to inherent toxicity nor to an antigen-antibody reaction (Jones, Carter and Rankin, 1954). It is reasonable to suppose that other mucopoly-

saccharides gaining entry to the body would be taken up by synovial tissue, remain in it for a long time and perhaps produce a cellular reaction.

Damage to tissues which are naturally antigenic can be produced by the action of an antibody prepared against them. In animals the production of nephritis or nephrosis by injecting anti-kidney serum is a familiar experiment, which is again artificial in that the antibody is prepared in an animal of a different species. An experimental model which is probably the result of an auto-immune reaction, and more likely therefore to have its counterpart in human pathology, is provided by iso-allergic encephalomyelitis. This disease of the central nervous system, reminiscent in many respects of disseminated sclerosis in man, appears a few weeks after an injection into the animal of a homogenate of brain or spinal cord prepared as a water-in-oil emulsion with liquid paraffin containing killed mycobacteria. The addition of these adjuvants is known to enhance antibody production and the lesions have been generally regarded as the outcome of an immunological reaction, though circulating antibodies have not been implicated.

The nervous tissue material used for injection may be derived from the same species or individual—or from an animal of different species. There is no counterpart to this mechanism in the connective tissues, although lesions in joints have been described in animals injected with a homogenate of spleen and adjuvants. The local reaction to these adjuvant emulsions in the tissues is intense and makes it difficult to assess the significance of lesions in joints proximal to the site of injection.

I have already referred to the antigenicity of two elements of the supporting tissues. It is not unlikely that nephritis in man may be due to immunologically determined damage to the glomerular basement membranes, but it is unjustifiable to assume that the reticulin antigen, which is well represented in synovial tissue, is, by reason of its antigenicity in another species, more likely than the inert components of connective tissue to participate in auto-immune reactions.

Auto-immune disease in man is most readily studied when it affects the cellular components of blood, and hæmolytic disease due to demonstrable antibodies is now a familiar phenomenon. Quite recently Hashimoto's disease of the thyroid has emerged as an auto-immune phenomenon. Antibodies to thyroglobulin can be produced by injecting it into an animal of the same species and the recipient may develop lesions resembling those of Hashimoto's disease (Rose and Witebsky, 1956). Furthermore, circulating antibodies have been identified in cases of this disease in man (Roitt *et al.*, 1956). Normally, according to Burnet (Burnet and Fenner, 1949), the native antigens of the body are recognized and ignored by the antibody-producing mechanism because they carry a 'self-marker'. Antibodies to a native antigen might result from stimulation of the antibody-producing cells either by an antigen which has for some reason lost its self-marker or by an antigen devoid of a marker but normally barred from access to these cells. There is

some evidence from iso-allergic encephalomyelitis, Hashimoto's disease and other phenomena that the antigens involved in auto-immune disease are often remarkable as being non-species-specific.

RESPONSE TO TREATMENT AND THE NATURAL HISTORY

Response to treatment.—The response of rheumatoid arthritis to treatment provides no promising clue to etiology. Gold, if indeed it has a specific effect, might be expected to inhibit the reaction of sulphydryl-dependent enzymes. Cortisone and its analogues alter many inflammatory reactions and their effect in rheumatoid arthritis cannot be regarded as specific.

Natural history.—According to Short *et al.* (1957), the risk of developing rheumatoid arthritis is the same at all ages from 15 onwards in men. In women they find an undue frequency of onset between 50 and 55 and a reduced susceptibility after 59. The survey conducted by the Empire Rheumatism Council (1950) showed that the risk of developing rheumatoid arthritis increases progressively from the age of 15 to 64 in single women but remains constant from 25 onwards in married women. In Denmark, Clemmesen and Arnsö (1952) found two peaks of prevalence in women: between 35 and 40 and between 45 and 55. It is generally agreed that rheumatoid arthritis is much less common in children than in adults. In various reports female sufferers from rheumatoid arthritis have been reported as accounting for 55 to 85 per cent. of the total cases.

GENETIC STUDIES AND ENVIRONMENT

Genetic studies.—It is generally accepted that rheumatoid arthritis is more common among the relatives of patients than those of unaffected controls. Patients with rheumatoid arthritis may recall relatives with the same disease more readily than unaffected individuals, and figures based on simple questioning of patients should be interpreted with caution. No genetic mechanism has been defined and more reliable data are likely to reach us only from field studies of family groups. Racial differences in susceptibility are likely to be recognized in the type of field investigation mentioned below.

Environment.—There is an old tradition (Clarke, 1915) that rheumatoid arthritis is never seen in the tropics. Cobb and Lawrence (1957) believe this to be untrue and maintain that there is reliable evidence neither of areas of freedom nor of undue prevalence. As a move towards a scientific study of environmental factors they have compared the incidence of rheumatoid arthritis in Leigh (Lancashire) and Pittsburgh and find the disease distinctly more prevalent in the English town where there is evidence of it in 11 per cent. of women of ages between 55 and 64. Much more information is needed before individual climatic and other environmental factors can be evaluated.

THEORIES OF ETIOLOGY

We now come to a consideration of the various theories of etiology based

upon the available evidence. For all practical purposes there are four worthy of mention: (i) infection and focal sepsis, (ii) metabolic abnormality, (iii) endocrine abnormality, (iv) hypersensitivity.

INFECTION AND FOCAL SEPSIS

The theory of direct invasion of the joints by an infective agent has found no recent supporting evidence and can be dismissed, though perhaps with an acknowledgement that a viral etiology is harder to exclude than bacterial infection. Interest in focal sepsis receded as the disappointments which followed its elimination in patients accumulated. Careful investigation failed to reveal any higher incidence of infected foci in patients with rheumatoid arthritis than in controls (Davidson, Duthie and Sugar, 1949). There is, however, some evidence that upper respiratory infection may act as a precipitating factor—perhaps determining no more than the time of onset of the disease—and Short *et al.* (1957) found that gonococcal infection figured unexpectedly often in the history of their patients.

METABOLIC ABNORMALITY

The florid inflammatory manifestations of gout remind us that inflammation can occur in a disease which springs from a disorder of metabolism, and Kellgren (1952) has assembled the evidence which favours a disruption of the collagen-polysaccharide complex as the initial lesion of rheumatoid arthritis. The lowered viscosity of the joint fluid in rheumatoid arthritis, indicating defective polymerization of its polysaccharide, has been regarded as evidence of an abnormality in connective-tissue metabolism (Ragan and Meyer, 1949).

ENDOCRINE ABNORMALITY

Clinical studies have provided some evidence that the endocrine system may play a part in rheumatoid arthritis, although changes in endocrine function may be secondary to the disease, or at most concerned with fluctuation in activity rather than with the basic etiology. The occurrence of remissions during pregnancy is well known and an association between the menopause and the onset of rheumatoid arthritis has often been suspected. The actual date of cessation of ovulation is rarely known and statistical proof of an association has been elusive. There is better evidence, according to Short *et al.* (1957), of an association between the disease and an artificially induced menopause. Several investigations have suggested a link between rheumatoid arthritis and the thyroid gland. After analysing their own observations and the literature on the subject Short and his colleagues conclude that a low basal metabolic rate is encountered unduly often in patients with rheumatoid arthritis, that this abnormality is not as a rule associated with clinical signs of myxœdema and that frank myxœdema is, in fact, uncommon. They suspect, on the contrary, that true hyperthyroidism may be relatively com-

mon in patients with rheumatoid arthritis. Thus, a link with thyroid abnormalities in general seems possible, but its nature is obscure and the arthritis rather than the thyroid abnormality may be the primary defect.

Rheumatoid arthritis starts more often during the winter months than in the summer. This may be a function of cyclical changes in pituitary function (known to occur in some animals) rather than an effect of environment. An investigation started in my department suggested that diurnal changes in pituitary activity may be related to fluctuation in the severity of some of the symptoms of rheumatoid arthritis, particularly stiffness and muscular weakness, throughout the twenty-four hours (Wright, 1957).

Selye has included rheumatoid arthritis among the diseases produced by the endocrine changes associated with 'stress', but his experimentally produced arthritis (Selye *et al.*, 1944) does not closely resemble the histological picture of rheumatoid arthritis. The role of physical or emotional stress is hard to evaluate—most clinicians are familiar with an apparent association between the onset of rheumatoid arthritis, or an exacerbation, and an event such as the death of a near relative. Statistically such disturbances occur no more often in patients than in unaffected individuals—but this does not mean that they cannot act as a trigger mechanism in susceptible people.

HYPERSENSITIVITY

This rather unsatisfactory term is used here to embrace a number of etiological theories which presuppose an altered reactivity of the body in the immunological sense. We have dwelt earlier on some of the lesions which can be produced by immunological manœuvres. We have seen, too, that auto-immune disease is an entity in man—and we know that the course of such diseases may be chronic and punctuated by exacerbations and remissions. There is, however, no direct evidence that any of the disturbances which are possible in theory are in fact operative in rheumatoid arthritis. The Rose-Waaler phenomenon is fairly specific, and we have seen that the rheumatoid factor has some of the attributes of an antibody to serum globulin. It would be premature, however, to try to fit the phenomenon into a formal theory of etiology. In lupus erythematosus we find evidence of another non-species-specific auto-immune antibody, and this disease, with its more consistently raised gamma globulin and its frequent association with hæmolytic anæmia, may be more likely to be an auto-immune process. The occurrence of a condition resembling rheumatoid arthritis in patients with agammaglobulinæmia (Janeway, Apt and Gitlin, 1953) has been cited as an argument against an immunological explanation for rheumatoid disease, although a few patients with acquired agammaglobulinæmia seem able to make the type of fixed tissue or cellular antibody which is responsible for delayed cutaneous hypersensitivity. It has been suggested that agammaglobulinæmia may itself be the result of an auto-immune process in which an antibody develops against the individual's own antibody-producing system.

CONCLUSION

None of the theories which I have mentioned rests on anything more than a few loosely connected pieces of evidence. I have devoted more space to the ways in which the machinery of immunity may go wrong than to possible metabolic or hormonal aberrations, only because my own interests have lain in that direction. A great deal of investigation, directed towards many aspects of the problem, is in progress, although its increasing momentum is still not commensurate with the size of the problem. It is not easy to predict the point at which a real break-through will occur and impossible on the basis of current theories of etiology to suggest any alternative to our present empirical approach to treatment.

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CORTICOSTEROID METABOLISM AND THE RHEUMATIC DISEASES

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THE title of this contribution calls for the discussion of two questions: (1) Is there any abnormality in the metabolism of corticosteroid hormones in the rheumatic diseases? (2) Given therapeutically, do these hormones affect the rheumatic diseases in any specific way?

CORTISOL AND THE METABOLISM OF CONNECTIVE TISSUE

The physiologically active corticosteroid hormones secreted by the human adrenal cortex are cortisol (hydrocortisone), corticosterone and aldosterone. As the administration of neither corticosterone nor aldosterone has any effect upon rheumatoid arthritis they will not be mentioned further. The answer then to the first question is sought in the metabolism of cortisol and in particular in its metabolism in connective tissues. We need to know whether the tissues receive an adequate supply of cortisol and whether there is any hindrance to its activity—in, for instance, rheumatoid arthritic tissues. Cortisol is known to exist in the blood in two forms: protein bound and free, the two being in equilibrium. There is little doubt that a similar state of affairs exists among the connective-tissue cells and fibres. The concentration of free cortisol available to the tissues will be determined by the concentration of free cortisol in the blood since the bound form is not freely diffusible. We need then to be able to measure the concentration of free cortisol in the blood but methods for such measurements are still in the experimental stage.

It *is* possible to measure fairly accurately the total cortisol: i.e., free plus protein-bound cortisol in blood. This is usually referred to as the 'plasma 17-hydroxy-corticosteroids' (17(OH)CS). It is sometimes misnamed 'free' to distinguish it from the reduced inactive glucuronide-conjugated 17(OH)CS in the plasma. The concentration of plasma 17(OH)CS has been regarded for some years as a measure of the available physiologically active cortisol but recently both Bush (1957) and Daughaday (1958) have shown that there is no simple relationship between the concentration of 'plasma 17(OH)CS' and the freely diffusible fraction.

Further, in pregnancy and possibly in a number of disease states alterations occur in the plasma proteins that bind cortisol. We do not yet know whether this binding is affected by the changes in plasma protein known to occur in rheumatoid arthritis and other connective-tissue diseases. It is of interest to note that prednisolone is not so readily bound as cortisol. This may explain why it is more potent, mg. for mg., and why it remains effective in the treatment of rheumatic disease for a much longer period than cortisone.

If the normal concentration of diffusible cortisol is able to reach the interstitial tissues, is it free there to exert its normal influence or is there

some hindrance to its free diffusion or effective concentration in the form, for instance, of an abnormal mucopolysaccharide? An attempt has been made by Hildegard Wilson (Wilson *et al.*, 1956) to follow the metabolism of cortisol in a connective-tissue space—the knee joint. She injected a suspension of cortisol into rheumatoid and normal knee joints and found that the metabolites formed differed in certain respects. Whether the difference was peculiar to the rheumatic type of arthritis was not established.

It is not yet known whether cortisol operates within or outside connective-tissue cells. If the latter there may be no metabolites resulting from its participation. (Hildegard Wilson's crystals of cortisol may have been taken up and metabolized by phagocytes.) The metabolites commonly measured in urine (17-ketogenic steroids, total 17-hydroxycorticosteroids, Porter-Silber '17-hydroxycorticosteroids') to assess the function of the adrenal cortex may well be formed almost entirely in the liver. They are excreted quantitatively in the same manner whether the tissues are in need of cortisol or not. They are usually a more accurate guide to the adrenal output of cortisol than the plasma concentration of '17(OH)CS' but no more reliable a guide to the concentration of diffusible cortisol available to the tissues.

In connexion with the adaptation that occurs during prolonged administration of cortisone and its analogues in rheumatoid arthritis, it must be remembered that these hormones have been given via the liver, and that the liver has been nicknamed 'the graveyard' of steroids. Normally the liver receives a low concentration of cortisol, most of which has first been through the other tissues of the body. When corticosteroids are given by mouth they pass through the liver in relatively high concentration before going anywhere else. As yet there has been no trial of aspirin versus cortisone or prednisolone with the latter given into the systemic, instead of the portal, circulation. The nearest approach has been a long-term study of the value of adrenal stimulation therapy for rheumatoid arthritics (West, 1957a).

Corticotrophin is given daily and following each injection the blood level of cortisol (entering the systemic circulation from the adrenal glands) rises for eighteen hours or so and then falls back again. As a critical level is passed the patient's stiffness and aches disappear, and as the level falls back towards the end of the day they reappear. For many rheumatoid patients this has occurred daily for several years without adaptation appearing.

It must be pointed out, of course, that sometimes the disease is too severe to be controlled by corticosteroid or any other therapy.

THE ACTION OF CORTICOSTEROIDS IN RHEUMATIC DISEASES

Many writers on this subject state that the effect of cortisone and its synthetic analogues upon rheumatoid arthritis is merely that of a non-specific anti-inflammatory agent. First we should ask just what the effects are that are referred to. The word inflammation is used to cover so many obviously different processes that it might be replaced by 'tissue response'. To state that cortisone is a non-specific 'anti-tissue response' agent invites the retort that this is a non-specific statement. High concentrations of cortisone are

known to inhibit some of the tissue responses to bacterial invaders but the invasion and tissue destruction go on. This action may be described as non-specific in so far as a number of bacteria are concerned. High concentrations of cortisone will also slow up or arrest normal healing, preventing the growth of granulation tissue. High concentrations will also produce measurable suppression of delayed allergic reactions such as that produced in the skin by tuberculin. The outstanding fact about the treatment of rheumatoid arthritis by cortisone is that for many patients a profound effect is produced, at least for a time, by a dose that will have no measurable effect upon bacterial inflammation, wound healing or the tuberculin reaction. In some patients on prednisolone therapy, instead of the destructive lesions spreading, as with bacterial invaders, bone erosions may be seen to heal. The fact that cortisone relieves the signs and symptoms of a number of rheumatic and para-rheumatic diseases does not mean that the action is not in some sense specific. Cortisone is known to play an essential part in many metabolic processes other than those directly concerned in the response to noxious foreign agents and injury. This is evident in the manifold deficiencies of the Addisonian patient.

CORTICOSTEROIDS AND GENESIS OF RHEUMATIC DISEASES

The epidemiology of rheumatoid arthritis suggests the existence of a ubiquitous environmental agent and an inherited factor which ante-dates our racial differences. The inherited factor is not a defect in the production of cortisol, although deficiency may bring the disease to light in a susceptible individual. I have been impressed by the small dose of prednisolone that will correct the disease in some rheumatoid patients who have a low adrenal output of cortisol. The fact that the disease process is so sensitive to changes in the concentration of circulating cortisol suggests that there is a local deficiency at the affected sites. This local deficiency may be absolute or relative. In the former case it could be due to the production locally of a substance that hinders the action of cortisol. In the latter case it could be that the local defect, perhaps involving an antigen-antibody reaction, can only be rendered innocuous by a higher than normal concentration of cortisol. In this connexion it is interesting to note that rheumatoid arthritis is not a stress to the hypothalamo-adenohypophysial corticotrophin-producing mechanism (West, 1957b). If it were, perhaps a rise in the adrenal output of cortisol might, at the start, prevent the establishment of the disease process.

Unfortunately it must be admitted that there are many patients with severe widespread rheumatoid arthritis for whom we cannot raise the local concentration of cortisol or prednisolone high enough to reverse the disease process without at the same time raising the levels elsewhere to such a degree that numerous other metabolic processes are either excessively damped down or excessively stimulated with resultant disorder either way. The disorders that result are not simply related to the dose given. For instance, corticosteroid-induced hypertension is largely dependent upon a

constitutional factor and corticosteroid-induced protein loss upon an inadequate food intake. There is also some evidence that in certain widespread connective-tissue and skin diseases much larger doses than usual are necessary to produce any 'side-effects'. These considerations all weigh against any simple explanation of the action of cortisone and its analogues (e.g. 'non-specific anti-tissue response').

THE FUTURE

Steroid studies have revealed much of the nature and chemistry of the corticosteroids and a lot of information concerning the ways in which these hormones are metabolized by the liver and by the enzymes existing within most cells. To further our knowledge of the rheumatic disease processes we want to find out whether there is a defect in the supply or metabolism of cortisol in the connective tissues. If there proves to be no such defect we shall need to discover just what abnormality in the tissues a raised concentration of cortisol corrects. We need to find out why, in the case of cortisol, the effect is so often short-lived and what advantages may be obtained by giving our new cortisone analogues for prolonged periods by a systemic route. During the early years of cortisone therapy it was commonly thought that the hormone's chemical structure was specific for its various actions and that it could not be altered without loss of effect. During recent years a large number of physiologically active cortisone analogues have been developed with various properties differentially enhanced or depressed. Some of these, in particular delta-1-cortisol (prednisolone), have proved to be of more value in the treatment of rheumatic diseases than cortisone. It is not unreasonable to look to the future for further worth-while developments. It is also not unreasonable to expect from further study of the modes of action and the metabolism of these hormones new knowledge that will enable us to reduce or abolish the side-effects and complications that now detract from their great value.

SUMMARY

Present knowledge of corticosteroid metabolism in relation to connective-tissue disease has been discussed and our ignorance exposed. The possible part played by cortisol in the mechanism of expression of rheumatoid arthritis has been considered and the concept that cortisone and its analogues play the role of non-specific anti-inflammatory agents challenged. It is concluded that these hormones have an established place in the treatment or correction of connective-tissue disorders and that it is necessary to go much further in our study of them and of their disposition and metabolism in the connective tissues.

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THE HORMONE TREATMENT OF RHEUMATOID ARTHRITIS

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In 1949 the discovery of the effects of cortisone and corticotrophin on patients with rheumatoid arthritis was announced from the Mayo Clinic by Hench, Kendall, Slocumb and Polly. This was accompanied by much publicity all over the world and such epithets as 'wonder drugs' were freely used. Subsequently it has been shown in trials extending over three years that the average early case (Joint Committee, 1957a) and the average later case (Empire Rheumatism Council, 1957) fare as well with aspirin as with cortisone. It has also become apparent that the prognosis in this disease is not as poor as was previously assumed. Kellgren, Lawrence and Aitken-Swan (1953), in a survey of rheumatic complaints in an urban population, found that 38 per cent. of women and 19 per cent. of men with rheumatoid arthritis had not even consulted their family doctors up to the time of the survey. More recently, Duthie, Brown, Knox and Thompson (1957) studied a large series of cases which were severe enough to be admitted to hospital and followed them carefully for six years after discharge. These authors report that of 247 cases in their series at the final assessment, 36 per cent. had marked restriction of function and were to some degree dependent upon others. A small group of these patients had been employed during the year preceding admission and of these 66 patients followed throughout, only 18 per cent. were incapable of work after six years.

It thus appears that in about 20 per cent. of patients with rheumatoid arthritis the outlook is poor with crippling as a possibility, and it is in this group that long-term hormone treatment must be considered.

SELECTION OF CASES FOR HORMONE TREATMENT

There are certain absolute contraindications, such as peptic ulcer, psychosis, psychoneurosis and diabetes mellitus, but these conditions are rarely associated with rheumatoid arthritis. Tuberculosis used to be in this list, but these hormones are now being used in the treatment of the pulmonary tuberculous, in combination with antibiotics. The main difficulty in the selection of cases is due to our inability to foretell whether a particular case of rheumatoid arthritis is going to be mild or severe. The natural history of the disease shows that periods of remission and of relapse occur, but again we cannot tell how long such episodes are likely to last.

It is wise therefore to try the effect of less drastic methods of treatment, such as periods of rest, both local and general, the exhibition of salicylates

in the highest tolerated dosage and possibly gold salt therapy before the use of steroids is considered. During this time it may be possible to gauge whether the case is one which is likely to end in crippling unless suppression with hormones is employed. On the other hand, it is important not to delay too long before starting treatment with corticosteroids for they will have no effect on joints which are deformed with contracted muscles and ligaments.

There are certain practical considerations which may determine the need for this treatment. If the patient is having increasing difficulty in continuing his work and so in earning a livelihood he is a candidate for hormones. If a housewife has lost the ability to close her hand this will soon become a permanent disability with a serious effect on her capacity to carry out her work. At an early stage this movement can be restored by the use of one or other of the corticosteroids. In fact, it is usually the purely practical aspect of each case which determines the starting of this form of treatment. Once the decision has been reached it should be made clear to the patient that the treatment will have to continue for a long period and possibly indefinitely and that medical supervision is necessary while taking these drugs.

Minor considerations to be taken into account are that women at the menopause are the most likely to suffer from side-effects and that men are less likely to do so than women.

DOSAGE

At the present time the lowest possible dose is employed which will enable the patient to regain independence. All attempts at a dramatic response are avoided. The effects of oral steroids last only a few hours and so it is important to spread the dose evenly throughout the day.

Cortisone.—The initial dose for adults should be 50 mg. a day. If there is no measurable response in a week the amount should be raised to 75 mg. a day. For short periods, to overcome stress or an exacerbation of the disease, up to 100 mg. a day can be given, but at this dosage side-effects will inevitably occur after a few weeks. Most patients will obtain suppression of the arthritis on 75 mg. a day or less, and if the dose has to be raised above this level for long it is doubtful if a long-term régime of treatment will be a practical proposition.

Hydrocortisone is the natural hormone produced in the largest amount by the adrenal cortex. By mouth it is slightly more potent than cortisone, but otherwise has no advantage except possibly for patients who have difficulty in keeping their weight down. It produces the same side-effects.

Prednisone and prednisolone are the analogues of cortisone and hydrocortisone. Early reports, when it was thought that these newer analogues were about three times as strong (Hart *et al.*, 1955; Joint Committee, 1957b), suggested their superiority as suppressive agents, but it is now established that their strength is five or even six times that of cortisone: i.e., the 5-mg. tablet has the same effect as 25 mg. of cortisone. The initial dose should be 10 mg. a day with a rise to 15 mg. if there is no response. It has been clearly shown by Black *et al.* (1957) that the incidence of severe side-

effects rises sharply with a maintenance dose of over 15 mg. a day.

These analogues were introduced by the manufacturers because they had less sodium-retaining effect than cortisone. This is undoubtedly true and in cases in which œdema occurs they are an improvement. Unfortunately they cause the other side-effects, and in the early days of their use it was suggested that they tended to produce more peptic ulcers than cortisone. Further studies have not yet confirmed this. It remains to be seen whether they will supplant cortisone as the most satisfactory oral corticosteroid, or whether other analogues with less liability to cause unpleasant effects will be produced.

MAINTENANCE THERAPY

In rheumatoid arthritis it has to be accepted that long and possibly indefinite administration is necessary in order to maintain suppression of the disease. It is imperative that the lowest dose which will restore independence should be found early in treatment. Only in this way will severe side-effects be avoided. As soon as it is clear that the hormones are proving effective the dose should be lowered slowly.

Cortisone and hydrocortisone are now available in 5-mg. tablets, and prednisone and prednisolone in 1-mg. tablets. These are useful when the dosage is being reduced to a maintenance level. Patients may have to accept minor degrees of disability in order to continue with prolonged treatment at a safe level of administration. The disease may go into remission during hormone therapy. The only way this can be recognized is by an absence of relapse when the dose is slowly reduced. It is wise to try a smaller dose every few months; if there is no relapse, withdrawal can be continued slowly.

COMPLICATIONS AND SIDE-EFFECTS

Sudden withdrawal of the hormones.—This gives rise to the most dangerous complications. During administration of corticosteroids the adrenal cortex goes into an involutionary or resting phase. If the hormones are stopped suddenly and this is accompanied by extra stress caused by an operation, an accident or a severe infection, the adrenal cortex may be unable to respond in the usual way by an extra secretion of steroids and adrenal failure with death may result. This has been reported on a number of occasions when these drugs have been stopped before minor operations.

In the early days of investigation surgeons were alarmed because experimental work in animals showed that wound healing was delayed by very large doses of these substances. They can now be reassured, as Popert and Davis (1958) have shown that their wounds will heal normally, but they should be warned that there is a real danger of postoperative collapse if the drugs are stopped. Likewise, during intercurrent infections or in the event of an accident the hormones must be continued. It has become current practice to increase the dose during such periods of extra stress. To cover operations or incidents in which the patient may be unable to swallow, intramuscular cortisone acetate is given in a dose of 100 mg. twenty-four hours

and one hour preoperatively and continued for a few days to provide an extra depot in case of adrenal failure.

Peptic ulcer is a side-effect feared by physicians controlling steroid therapy. Because dyspepsia is often slight while patients are on this treatment the first indication of trouble may be a hæmorrhage or perforation. Minor degrees of indigestion must be taken seriously and investigations should be carried out to confirm or exclude ulceration. Small peptic ulcers will heal if treated medically without necessarily withdrawing the hormones.

Excessive gain in weight often occurs in women on this régime. Because of the increased appetite the weight loss accompanying rheumatoid arthritis is quickly abolished and obesity may follow. It must be checked by dieting as it may cause foot or knee strain which can nullify the improvement brought about by the steroids.

Rounding of the face (*moon face*).—In women this is an almost constant accompaniment of long-term steroid treatment. It is usually not severe and may disappear after a time. Patients whose independence has been restored will accept it as a necessary complication of their treatment. If not, the only solution is withdrawal of the drug and relapse of their arthritis.

Osteoporosis is caused by severe rheumatoid arthritis and may be increased in these cases by the effect of hormones. In some cases on high dosage fractures have occurred.

Other side-effects which have been reported are hypertension, reactivation of a tuberculosis focus and psychological disturbances.

ROUTINE SUPERVISION OF CASES ON HORMONE TREATMENT

It is necessary to see such patients regularly in order to determine whether the steroids are suppressing the disease and to discover any side-effects at an early stage. The assessment of rheumatoid arthritis is not easy because so many of the signs, such as stiffness and lassitude, are subjective. The patient's ability to work, dress or get in and out of a bath will often give a good indication of the effectiveness of treatment. Weight and blood pressure should be checked, and œdema and glycosuria be excluded. Approximate measurements of tenderness of affected joints and the strength of grip shown by a rolled sphygmomanometer cuff can be helpful. It is usual to allow these patients to take simple analgesics such as aspirin as they require them. Some manufacturers have provided combined tablets of salicylate and a small quantity of cortisone, prednisone or prednisolone. There seems to be no particular advantage in these expensive combinations as they are not usually in the most advantageous proportions.

These patients should be asked about dyspepsia and, as already stressed, if present this should be treated seriously. It is wise to have a chest x-ray every six months to exclude any tendency to reactivation of an old tuberculous focus.

LOCAL HYDROCORTISONE

Local hydrocortisone has proved a useful adjunct to treatment in rheumatoid

arthritis. Hydrocortisone acetate and its analogue, prednisolone acetate, have a marked anti-inflammatory action when placed intra-articularly. Hollander *et al.* (1951) showed that there was a reduction in leucocytes and a rise in the viscosity of joint effusions within a few hours. Such injections should be made under strictly aseptic conditions.

The most favourable joint is the knee where the aspiration of an effusion and the introduction of 50 mg. (2 ml.) of hydrocortisone is strikingly effective. This will usually have to be repeated as the effect is not long-lasting. Other joints in rheumatoid arthritis which are feasible for injection, if inflamed and distended, are the wrists, ankles and elbows. In non-weight-bearing joints the anti-inflammatory effect lasts longer.

CORTICOTROPHIN

It is often assumed that treatment with corticotrophin is the same as with cortisone or its analogues. This is not so. Administration of oral steroids results in involution of the adrenal cortex, whereas corticotrophin stimulates the cortex to secrete more than the normal amount of the naturally occurring steroids, principally hydrocortisone and corticosterone. This treatment, however, can only be given by daily subcutaneous self-injection. Recently we (Savage *et al.*, 1957) have shown that such therapy can be controlled by the chemical estimation of 17-hydroxycorticosteroids (17(OH)CS) in urine as well as by the clinical measurements previously mentioned.

For short courses of treatment, to cover manipulation or a concentrated period of rehabilitation, corticotrophin has the advantage that the adrenal cortex is left active and enlarged on withdrawal of the drug rather than involuted as after cortisone. Without biochemical control it is impossible to tell the degree of adrenal stimulation produced by a given dose, but 20 units daily of a long-acting preparation of corticotrophin will usually suppress an inflammatory reaction.

RESULTS

Cortisone and its analogues have now been available for treatment in severe cases of rheumatoid arthritis long enough for the publication of a number of reports from all over the world. Series of cases treated with satisfactory results on a long-term programme have been announced from the United States, France and Denmark. In this country Copeman *et al.* (1954), observing 20 severe cases who had lost their independence and had failed to respond to other methods of treatment, found with prolonged cortisone administration that 17 were improved to such an extent that they returned to a working life. More recently, Fearnley *et al.* (1957) have reported favourably on a group of patients with severe rheumatoid arthritis treated over a two-year period with prednisone. A number of patients in this country have now had cortisone and the newer oral steroids, prednisone and prednisolone, for over six years continuously. This has enabled the men to return to, and to continue, gainful employment and the housewives to continue their work. The

disadvantage of this form of treatment is that it does not cure the disease and that it necessitates constant medical supervision.

THE FUTURE

Although cortisone has now been available for research for eight years we still do not know its mode of action. Effective as it is in suppressing the symptoms and signs of rheumatoid arthritis there is no evidence of abnormality of the adrenal cortex in this disease. The present methods for estimating adrenal activity are still unsatisfactory, although considerable progress has been made in knowledge of steroid metabolism. It is known that the normal adrenal cortex secretes about 35 mg. of hydrocortisone daily, and that there is a diurnal variation of the blood hydrocortisones throughout the day. The mean value is high at 8 a.m. and falls during the morning. After a short rise it falls again between 4 p.m. and 6 p.m. and is lowest at 3 a.m. before rising to the morning peak. Further biochemical research may well make available a practical method of measuring steroid levels in health and disease so that the regulation of dosage can be by scientific calculation, rather than the present method of balancing clinical improvement against side-effects.

Pharmaceutical research is constantly endeavouring to produce oral steroids which will have an anti-inflammatory and anti-rheumatic effect without the disadvantage of side-effects. Many have already been tried and the possible permutations of the steroid nucleus are considerable.

SUMMARY

(1) Treatment of rheumatoid arthritis with corticosteroid hormones should only be considered in the minority of cases: about 20 per cent.

(2) It should only be employed in the few severe cases in which other methods have failed to halt the disease.

(3) Supervision is necessary for all patients undergoing such treatment.

(4) The most serious side-effects are peptic ulceration and the complications of sudden withdrawal of the hormone.

(5) With continuous treatment it is possible to prevent crippling in some patients and to restore independence in others.

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THE PRESENT STATUS OF PHENYLBUTAZONE THERAPY IN RHEUMATIC DISEASE

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IT is now 12 years since phenylbutazone ('butazolidin'; 1 : 2 diphenyl-4-*n*-butylpyrazolidine-3 : 5-dione) was synthesized, and seven years since the first clinical results were published (Currie, 1951). A comprehensive review of the earlier literature on the drug was given by Hart (1953) in this journal five years ago. Since then the use of phenylbutazone-amidopyrine compounds, such as 'irgapyrin', have been almost entirely abandoned in this country. The intramuscular route has also been superseded by the oral administration of 100-mg. or 200-mg. tablets. A high dose régime of 600 mg. or more a day has also been given up. Bruck *et al.* (1954) demonstrated that a blood level of 10 mg. per cent. represents the optimum therapeutic concentration and that beyond this level no further therapeutic benefit is obtained whilst the incidence of toxic effects rises steeply. The development of a reliable colorimetric method for estimating blood levels (Pulver, 1950) provides a useful check in controlling the dose when necessary, and has put the effective and safe administration of phenylbutazone on a proper footing.

THERAPEUTIC EFFECTS

Analgesic and anti-inflammatory.—Although animal experiments (Domenjoz, 1952) have provided evidence of an anti-inflammatory effect of this substance, there is little support for the view that its main therapeutic effect is mediated by anything other than its analgesic property (Mason, 1953). It is slowly absorbed, taking some hours to reach 10 mg. per cent. concentration in the blood, but maintains a constant blood level thereafter when taken three times daily. This renders it more suitable for chronic painful conditions than for the more transient pain such as headache or toothache. Yet it must be admitted that there seems a curious predilection for locomotor pains, and even within these it is more effective for some than for others. Thus, spondylitic pain responds almost specifically and acute gout likewise. Encouraging reports have also appeared of its value in superficial thrombophlebitis, in which its anti-inflammatory effect may be manifest (Stein, 1955; Gillespy, 1957; Elder and Armstrong, 1957).

Uricosuric.—Phenylbutazone has no more than a slight uricosuric effect,

which may be neutralized if considerable water retention occurs at the same time (Mason, 1954). Indeed, Yü and Gutman (1955) suggest that with blood levels below 10 mg. per cent. it may lead to urate retention.

Studies of the metabolites of phenylbutazone have produced some interesting substances: a phenol (G.27.202) and an alcohol derivative (G.28.231), the former showing marked anti-inflammatory and analgesic properties but causing sodium retention, and the latter a moderate uricosuric but little analgesic effect. This uricosuria was enhanced by substituting the butyl side-chain with a phenylthioethyl group (G.25.671) which produces a sulphoxy derivative in the urine (G.28.315). The latter appears to be the most potent uricosuric substance known to date, increasing the urate clearance by the kidney some seven times compared with phenylbutazone which increases it three times, probenecid which increases it four to five times, and salicylates which increase it four times, without causing sodium retention (Burns *et al.*, 1957; Ogryzlo and Harrison, 1957).

Clearly there are considerable potentialities in the development of the rather weak uricosuric effect of phenylbutazone.

CLINICAL APPLICATIONS

Before dogmatizing on the present status of phenylbutazone in rheumatic disease we felt it would be informative to study our clinical material at the London Hospital to see what use we are in fact making of phenylbutazone at the present time, with special reference to its use in rheumatoid arthritis. Only in the case of rheumatoid arthritis are our cases in sufficient numbers to enable an adequate analysis to be made.

Rheumatoid arthritis.—A sample of 335 cases of rheumatoid arthritis, representing all the patients with this disease seen during a three-month period, was reviewed. We found that of these no fewer than 225 (165 females and 60 males), or 67.2 per cent., had at some time been prescribed phenylbutazone by us. As might be expected with a new drug of this nature there was a tendency in the earlier years to prescribe phenylbutazone for the more chronic case; thus, of those for whom the drug was prescribed in 1952 only 22 per cent. had a disease duration of less than three years, whilst in 1955 and 1957 70 per cent. and 68 per cent. respectively had a history of less than three years. In other words we are now tending to prescribe the drug earlier in the course of the disease. In 167 (74 per cent.) the dose never exceeded 400 mg. a day; since 1954 only an occasional patient has had a higher dose than this: five patients had been given between 800 and 1,200 mg. a day—all before 1953. Evidently we have found, with others, that 400 mg. a day is the maximum dose and it has now moved up to second on our list, after aspirin, of possible drugs for the routine hospital outpatient with this disease.

Ankylosing spondylitis.—We believe that phenylbutazone should normally be given a trial before embarking on deep x-ray therapy in ankylosing spondylitis, especially in view of the evidence (Court Brown and Abbatt, 1955; Abbatt and Lea, 1956) that irradiation of the spine places the patient in a significantly higher risk category for leukæmia than the normal population, certainly after a second course of deep x-ray therapy. Whether or not the drug influences the natural history is doubtful and very careful clinical

and radiological supervision is necessary so that radiotherapy, which probably does influence the natural history favourably (Sharp and Easson, 1954), can be applied if progression of the disease threatens the patient's functional capacity or general health. It is also particularly useful for women of childbearing age. Unfortunately, the 10 per cent. or more incidence of peptic ulceration in ankylosing spondylitis may preclude its use. On the other hand, we have the impression that smaller doses of the drug are more effective in this disease than in others, many patients being controlled with 200 mg. or, not infrequently, 100 mg. a day.

Osteoarthritis.—Phenylbutazone is of especial value in osteoarthritis of the hip where, by permitting the proper use of the joint in allowing smoother walking, it may prevent the development of contracture and deformity. Nocturnal pain is also conveniently relieved owing to its prolonged action. In other forms of osteoarthritis, however, the symptoms are often insufficient to justify its use.

Gout.—The value of phenylbutazone in acute gout is now accepted (Kuzell *et al.*, 1954; Wilson *et al.*, 1956). Although the exact mechanism of its action is unknown it may well supersede colchicine for the majority of patients. This is the only condition for which we now use a dose in excess of 400 mg. a day, preferring 600 mg. a day until the acute attack is controlled, usually within two to three days, after which 400 mg. a day is sufficient until the attack has completely subsided. It is especially valuable if colchicine is ineffective because therapeutic doses are prevented by gastro-intestinal upset. In the later chronic stages of gout when complete remissions between attacks are not occurring, small doses of phenylbutazone, as used in rheumatoid arthritis, are also valuable. The use of uricosuric agents, such as probenecid, however, and possibly in the near future the phenylbutazone derivatives previously mentioned, will probably replace phenylbutazone itself for interval therapy although not for the acute paroxysm.

Miscellaneous rheumatic diseases.—Phenylbutazone may be of value in other arthropathies or bone disease. Psoriatic arthritis behaves similarly to rheumatoid arthritis; the joint manifestations of Reiter's disease appear to be responsive, especially the plantar fasciitis which may be very effectively controlled; the pain of Paget's disease may also be relieved most effectively, and in certain cases it may fill a useful gap between aspirin and opium for secondary malignant deposits in bone. We are not able to assess its value in acute disc protrusions. Steer (1956) and others have reported uncontrolled observations and commented favourably. A multicentre controlled trial is at present being conducted to study this aspect.

TOXIC EFFECTS

As so often happens when a widely used drug produces occasional serious toxic effects the literature tends to give an unbalanced view, since there is a natural tendency to report serious toxicity without relating it to the total number of cases being treated. Our experience of the toxic effects of phenyl-

butazone is shown in table I. Two-thirds of the patients with rheumatoid arthritis appear to tolerate the drug satisfactorily. It is interesting to note that these patients showed a better symptomatic response than the remaining one-third who developed toxic reactions (table II). Thus, 87.8 per cent. of

	No.	Percentage
No intolerance	136	
Transient intolerance, drug continued	11	
	147	65.3
Toxic reactions:		
Gastro-intestinal	45	20.0
Rash	18	8.0
Buccal ulcers, Stomatitis, Sore throat	7	3.1
Œdema	5	2.2
Headache/vertigo	3	1.4
	78	34.7

TABLE I.—Toxic reactions in 225 patients with rheumatoid arthritis.

the non-toxic group claimed some symptomatic relief compared with 60.3 per cent. of the toxic group, whilst 42.2 per cent. of the former and only 16.7 per cent. of the latter had excellent or good relief. The majority (two-thirds) of toxic reactions were gastro-intestinal. One-quarter developed a

Response	Non-toxic group		Toxic group	
	No.	Percentage	No.	Percentage
Excellent	7	4.8	0	
Good	55	37.4	13	16.7
Fair	67	45.6	34	43.6
Nil	18	12.2	31	39.7
Total	147		78	

TABLE II.—Subjective therapeutic response in 225 patients with rheumatoid arthritis.

rash, whilst buccal ulceration and stomatitis were relatively uncommon. No blood dyscrasias were noted in this series, but we have had one fatality which, by the nature of this inquiry, could not be included—a case of hypersensitivity already reported by O'Brien and Storey (1954).

In general, toxic effects appeared early. In our group 12 occurred in the first week, 21 in the next three weeks and 14 in the next two weeks; 60 per cent. of the toxic reactions therefore appeared in the first six weeks of administration. Among these were nearly all the cases of rash, stomatitis, buccal ulcers, œdema and vertigo. The onset of gastro-intestinal reactions,

however, was often more delayed: 16 patients developed gastro-intestinal effects after six months to four years of continuous phenylbutazone therapy. Among the latter were three confirmed cases of peptic ulceration occurring after two years' medication, and one male was admitted with acute ulcerative colitis after 15 months' therapy. We feel that the drug should be discontinued as soon as there is any apparent toxicity, no matter how long the patient has been taking the drug, and that it is wise to abandon its use for that particular patient rather than resume its administration, even 'cautiously', when the symptoms have settled down.

In view of the possibility that the administration of a potentially toxic drug would be more likely to produce ill-effects if the patient was already 'toxic' from chronic inflammatory disease such as rheumatoid arthritis, we compared the over-all toxicity rate in a non-rheumatoid sample. This consisted of 71 patients attending the clinic at the same time who had been prescribed phenylbutazone. They consisted mainly of patients with ankylosing spondylitis and osteoarthritis, with a few cases each of psoriatic arthritis, Reiter's disease, gout, Paget's disease and cervical or lumbar disc lesions. Of this control group, 23, or 32.4 per cent., suffered toxic reactions severe enough to warrant the withdrawal of phenylbutazone, a figure strictly comparable with the rheumatoid group. The distribution of the various toxic effects was much the same as in the rheumatoid group.

Other toxic reactions ascribed to phenylbutazone have been hepatic necrosis and other visceral lesions reported by MacCarthy and Jackson (1955), and Stevens-Johnson syndrome and granulocytopenia by Steel and Moffatt (1954), whilst a report of a fatal case with multiple toxic effects, including polyneuritis, was given by Fraser (1955). Venning (1957) has reported a case of aplastic anæmia following phenylbutazone therapy. Linsk *et al.* (1957) have recently reported that phenylbutazone may have a transient depressant action on the thyroid gland and Morgans and Trotter (1955) report one case in which thyroid enlargement occurred.

Unfortunately, low dosage is not the whole answer to preventing serious reactions, and among the reported fatal cases are some in which the maximum dose never exceeded 400 mg. a day. Others, however, e.g., Smyth and Clark (1957), agree with us that there is evidence that keeping the maximum dose to 400 mg. daily lessens the incidence of toxicity. It is better for the drug to be taken on a full stomach, whilst it need hardly be restated that patients should be watched with care and told to report immediately if there are any untoward symptoms. We do not, however, carry out routine blood counts except in so far as they appear to be indicated on clinical grounds. We avoid its use in patients with disturbed cardiac function; in particular, the action of phenylbutazone in causing reduced output of sodium and water retention must be borne in mind as patients with evidence of cardiac disease may become decompensated after taking the drug. We also withhold it in patients with hepatic or renal insufficiency, when there is disease of the gastro-intestinal tract, especially peptic ulcera-

tion, when previous drug sensitivity has been shown, and when there is any evidence, past or present, of blood dyscrasia. From our figures, however, it is clear that these contraindications do not prevent its use in a high proportion of patients.

CONCLUSION

Our therapeutic armamentarium of useful, as opposed to useless, drugs in the treatment of rheumatic disease remains distressingly small. In the treatment of a chronic disease it is often necessary to 'ring the changes', either because of the unfolding natural history of the disease or because of the ineffectiveness of, or intolerance to, the particular drug being used at the time. Phenylbutazone, or its newer variants, will remain valuable in the management of these chronic painful diseases until the time that a drug which will actually influence the natural history of the disease process is discovered. Indeed, we believe that the potentialities of the pyrazolidin complex have not yet been fully exploited, and that further work should be pursued just as it is with variations of the steroid molecule. It is by no means certain that a potent steroid molecule can be produced which will retain anti-inflammatory potency without producing at the same time profound metabolic side-effects. It should not be forgotten that, despite the occasional toxicity of phenylbutazone, this substance is at least free from such effects.

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THE TREATMENT OF OSTEOARTHRITIS

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OSTEOARTHRITIS is a degenerative condition and therefore any treatment given is unlikely to produce a cure; all that can be hoped for is a remission of symptoms. Bearing this limitation in mind, treatment of osteoarthritis is surprisingly successful. Fully one-half of the patients attending the physical medicine or rheumatism department have symptoms derived from osteoarthritis, and it is therefore an important subject when considering the treatment of locomotor diseases.

THE IMPORTANCE OF ACCURATE DIAGNOSIS

It is necessary in the first place to be satisfied about the 'pathological' diagnosis: to be certain, for instance, that one is not dealing with a rheumatoid, gouty, or other type of arthritis. Secondly, and almost as important, it is necessary to be clear as to the 'anatomical' diagnosis: i.e. the morbid process responsible for the production of the symptom of which the patient is complaining. Pain is a leading symptom in osteoarthritis, and is probably the most frequent cause for seeking medical advice. The physician should seek to determine, from his clinical and radiological examination, the tissue responsible for its production.

Acute inflammatory episodes occur in osteoarthritis, and in these there is a constant, severe and deep-seated pain situated over the affected joint which is hot and swollen. The pain in cases with *marked capsular fibrosis* is one that occurs at the extremes of movement, and is reproduced by putting the joint through its full range. Frequently, *muscular weakness and wasting* accompanying osteoarthritis are the cause of much pain. In these cases the pain comes on after a little exercise, and is often felt in the muscles near the affected joint. It is relieved by rest. This type of pain occurs almost exclusively in the weight-bearing joints (spine, hip, knee, ankle and feet), and is naturally accompanied by much muscular wasting and diminution in the muscle bulk around the joint. *Loose bodies* in the joint may lead to acute inflammatory episodes, but it is often only possible to be satisfied about their presence after an x-ray.

Osteoarthritis is predominantly seen in weight-bearing joints and in joints that have been the site of injury or previous disease. The condition also occurs as a familial and inherited one in women and affects the terminal interphalangeal joint of the fingers (Stecher, 1955). Probably the majority

of cases of osteoarthritis occur in the cervical and lumbar spine, and these present the greatest difficulty in treatment.

CERVICAL SPONDYLOSIS

Cervical spondylosis, or, as it was formerly called, 'osteoarthritis of the cervical spine', can reveal its presence by symptoms confined to the neck (stiffness or pain) or there may be symptoms in the neck and referred to the back of the head, the face, the shoulder region, or down one or both arms to the fingers.

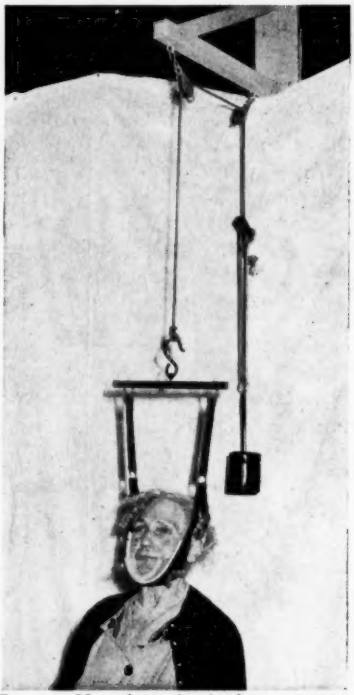

FIG. 1.—Use of traction in the treatment of cervical spondylosis.

Treatment of cervical spondylosis is dictated by the nature of the physical signs and the radiological appearances. If the neck is found to be very stiff, the treatment designed to correct this abnormality should relieve the symptoms. On the other hand, supposing the pain is one that comes on at rest when the muscles are relaxed, it is reasonable to assume that this is due to wasted muscles and, because of the loss of their ability to support the cervical joints by their normal elasticity, there is untoward movement occurring in the region of the intervertebral discs. This leads to pressure symptoms from osteophytic outgrowths touching the cervical nerve roots as they proceed through the intervertebral foramina. Patients with stiff necks should be given some form of heat in order to relieve their pain, and neck exercises to restore normal neck mobility. Patients with stiff necks and with pain referred down the arm or over the head are often relieved by traction to the cervical spine by means of a head halter (fig. 1). Those with pain especially coming on at night, and particularly those in whom there is little or no restriction of movement, respond best to 'labile' or 'roller' faradism. This form of faradism is given with one of the electrodes connected to a roller, and the erector spinæ muscles are stimulated as the roller is moved up and down. Because of the varying lengths and sites of insertion of the intricate and complicated nature of the muscles being treated, the normal form of faradism with pads and electrodes in two fixed places is nothing like so effective.

LUMBAR SPONDYLOSIS

Lumbar spondylosis is probably one of the most important causes of locomotor disability in the older age-groups. Often there is, in addition to back pain, sciatica with wasting of the muscles of the thigh and sometimes of the calf, and paræsthesia travelling down into the toes of the affected leg.

FIG. 2.—Use of traction in the treatment of lumbar spondylosis.

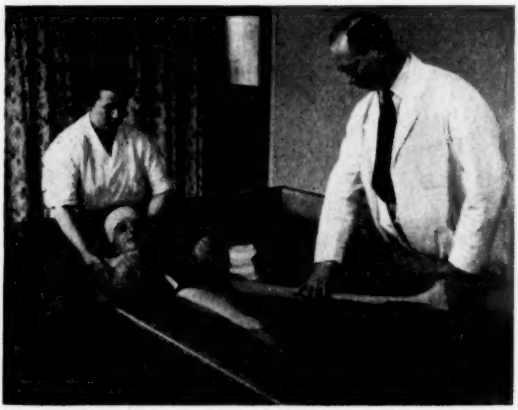

FIG. 3.—Exercises in water in the treatment of osteoarthritis.

There is no cut and dried treatment for lumbar spondylosis. Each patient's treatment has to be decided on the history and physical signs present. Those with stiff lumbar spines are usually successfully treated with conventional or short-wave diathermy and extension exercises. Extension exercises are of great importance in the permanent relief of symptoms and should be persisted in even after symptoms have been completely relieved. Traction on the lumbar spine is also a very successful method of treatment (fig. 2), and this should also be combined with extension exercises, which can be done once the traction has been taken off. Elderly patients who have other large joints affected, apart from the lumbar spine, often do very well when given gentle exercises in water; in these cases the use of a Hubbard tank is ideal (fig. 3). Any patient with lumbar spondylosis and sciatica who does not respond after a few treatments should be put to bed and rested on his back. Fracture boards should be used to prevent

the bed sagging. Even when resting in bed he should be given gentle extension exercises.

Unfortunately it is true to say that patients with lumbar spondylosis have a strong tendency to relapse and, especially in the older age-groups, the prescription of a lumbo-sacral corset should be considered.

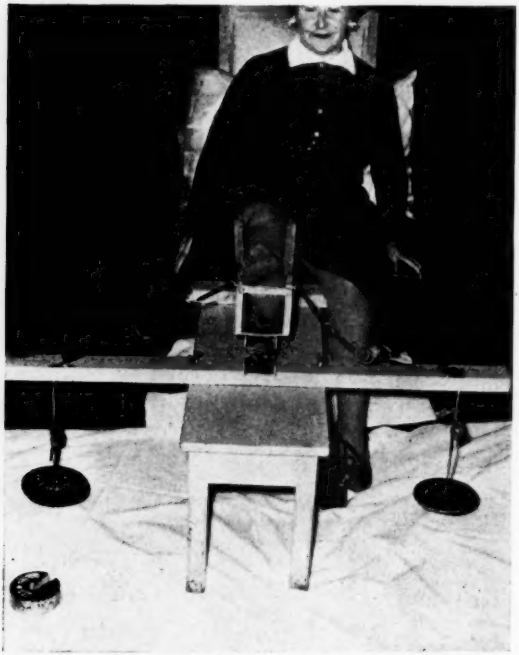

FIG. 4.—Use of hip-rotating exerciser in the treatment of osteoarthritis of the hip.

OSTEOARTHRITIS OF THE HIPS

Osteoarthritis of the hips is probably one of the severest and most disabling forms of arthritis. The symptoms are usually due to muscle weakness or to capsular fibrosis.

Muscle weakness.—In the case of patients with marked wasting of the quadriceps and gluteal muscles, attention should be directed to these muscles with a view to strengthening them by faradism and exercises. De Lorme and Watkins (1951) have described their method of exercises against progressive resistance. The strength of the muscle being treated is measured each week by asking the patient to lift the maximum possible weight. This weight is divided by two-thirds, and the patient is asked to lift this thirty times a day. The following week the patient is again tested and the same procedure adopted. A convenient way of carrying out these progressive resistance exercises for the quadriceps at home is as follows:—

Wear an old pair of shoes with a hook screwed into the back of the heel. Take an earthenware hot-water bottle and tie a piece of string around the knob at the top of the bottle. Hang the empty hot-water bottle from the hook at the back of the heel. Sit on the edge of the kitchen table or other high table, swinging the leg so that the leg is straight at the knee. Do this thirty times. When this can be done easily, fill the bottle one-quarter full and do the same exercise. As the leg gets stronger fill the bottle up progressively. When the exercise can be done with the bottle full of water, do the same thing with the bottle filled progressively with lead shot.

Capsular fibrosis.—One of the most successful orthopædic operations for osteoarthritis of the hip has been the subtrochanteric osteotomy. This involves dividing the femur below the lesser trochanter; the pain is relieved, even though the weight is still passing through the affected osteoarthritic hip, presumably by the relief of tension on the posterior aspect of the capsule of the hip joint.

One of the first deformities arising in hip-joint disease is for the patient to start walking with the foot everted on the affected side. A hip-rotating exerciser (fig. 4) was therefore designed and has been found very helpful in relieving the pain and in restoring rotatory movements to osteoarthritic hip joints. Short-wave diathermy to the hip is, of course, one of the standard and one of the most successful pain-relieving treatments and, if this is combined with quadriceps exercises or hip rotation exercises as described, the results are often surprisingly successful.

OSTEOARTHRITIS OF THE KNEES

Osteoarthritis of the knees is one of the most common causes of pain in patients attending the physical medicine or rheumatism department. It can be due to either pathological changes in the capsule of the joint or to muscle weakness associated with the arthritis.

Capsular changes.—These patients should be treated with short-wave diathermy to the knee and mobilizing exercises.

Muscle weakness.—Patients with muscle weakness should be treated with faradism to the quadriceps and progressive resistance exercises.

OSTEOARTHRITIS OF THE ANKLES AND TARSI

These patients are treated in a similar way to those with osteoarthritis of the knees, but those with severe tarsal osteoarthritis will require special surgical walking shoes with comfortable sponge rubber insoles.

OSTEOARTHRITIS OF THE SMALL JOINTS OF THE HANDS

Osteoarthritis chiefly affects the carpo-metacarpal joints of the thumbs and the terminal interphalangeal joints of the fingers. As has already been pointed out, the latter is an inherited and familial complaint in women. The carpo-metacarpal joints of the thumbs are often successfully relieved with small intra-articular injections of hydrocortisone. This is given through the dorso-lateral aspect of the joint, and often one injection is sufficient. The usual dose required is 12.5 mg.

Heberden's nodes, or osteoarthritis of the terminal interphalangeal joints, is often very resistant to treatment. The best that can be achieved is the relief of pain and the preservation of some mobility, but it should be pointed out to the patient that this is an inherited and degenerative condition, and that it is impossible to restore the hand to its former appearance. Occurring in women as they do, these nodes are often the source of irritation and

distress, and cause difficulty in sewing, and the like, because of the trouble in wearing a thimble. Wax and exercises are useful in the acute stage to a limited extent but, if the condition is severe enough and really troublesome, it might be advisable to ask a surgeon to perform an arthroplasty on the joint.

OBESITY, DRUGS, AND CAPACITY FOR WORK

Osteoarthritis and obesity.—It is not the purpose of this article to go into details over the treatment of obesity, but it does require to be stressed that there are few conditions in medicine in which weight reduction is of equal importance. Even the loss of a few pounds can have a most beneficial effect in persons in whom the weight-bearing joints are affected.

Analgesic drugs.—These have a place to play in the relief of pain in osteoarthritis in almost all cases, and the amount taken daily is a good indication of the severity of the symptom.

Work and earning capacity.—Osteoarthritis can be a most disabling and chronic condition, and in consequence it gives rise to some of the most difficult social problems. If the patient can possibly get back to his old job, he is far better advised to attempt this than to undertake something new. It is outside the scope of this article to go into the problems of social medicine in connexion with osteoarthritis, but the almoner should keep in touch with patients from their first visit to hospital.

SUMMARY

Osteoarthritis is a common condition with an underlying degenerative cause which is as yet unknown. Treatment must therefore be directed to the relief of pain and the accompanying disability. Accurate localization of the site of origin of symptoms is an essential prerequisite to treatment, which consists largely of physiotherapy, the prescription of analgesic drugs and, in advanced cases, orthopædic surgery. The social implications of this condition are often important.

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THE TREATMENT AND PREVENTION OF RHEUMATIC FEVER

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RHEUMATIC fever is one of the complications of group A β-hæmolytic streptococcal sore throat. Were it not for the carditis of the acute stage, and even more for the valvular lesions which appear gradually in the years that follow, rheumatic fever would be of little more account than the sore throat from which it springs. The rheumatism and the fever are short-lived and easily controlled by salicylates and, as a general rule, there are no residual joint lesions. Apart therefore from symptomatic treatment directed towards the relief of pain and the abolition of fever, the therapeutic attack on rheumatic fever is directed towards the prevention of cardiac damage. This may be attempted at several points in the long chain of events leading to rheumatic heart disease (fig. 1). Take, for instance, a patient in whom several attacks of rheumatic fever have led to mitral stenosis. She has passed through several stages, at each of which there is some hope of preventing further damage. Originally this patient contracted from someone else a streptococcal infection: this could have been avoided by adequate segregation, or by prophylactic antibiotic. Having developed a streptococcal tonsillitis, the subsequent rheumatic fever could have been avoided by prompt and adequate antibiotic treatment of the sore throat. Having developed rheumatic fever, the severity of the subsequent carditis could have been mitigated, we believe, by prolonged bed rest. Or possibly, as some people believe, by salicylates or hormone therapy in addition. Following recovery, further rheumatic attacks and further cardiac damage could have been avoided by regular daily penicillin prophylaxis. Finally, we believe that one day we shall learn enough about the long drawn-out process of fibrosis to prevent the gradual deformity which over the course of years follows in the wake of the acute endocardial damage and produces the ultimate crippling and failure.

THE PREVENTION OF CHRONIC VALVULAR DEFORMITY

There are two main theories to account for the development of chronic deformities of the mitral or aortic valves in the years following an attack of rheumatic fever: one postulates progressive and chronic fibrosis in the substance of the valve and valve ring, due to continuing inflammatory disease; the other postulates superficial accretion of platelet thrombi (Bland and Jones, 1951) or fibrin (Magarey, 1951) on damaged endothelial surfaces, with later organization.

Evidence has recently accrued that the histological rheumatic process remains active in the connective tissue of the heart for long periods after the subsidence of clinical activity. In almost all of a now numerous series of left

atrial biopsies taken at mitral valvulotomy, Aschoff bodies have been found in nearly half the cases, although clinical evidence of activity has been absent before operation, and the sedimentation rate has been within normal

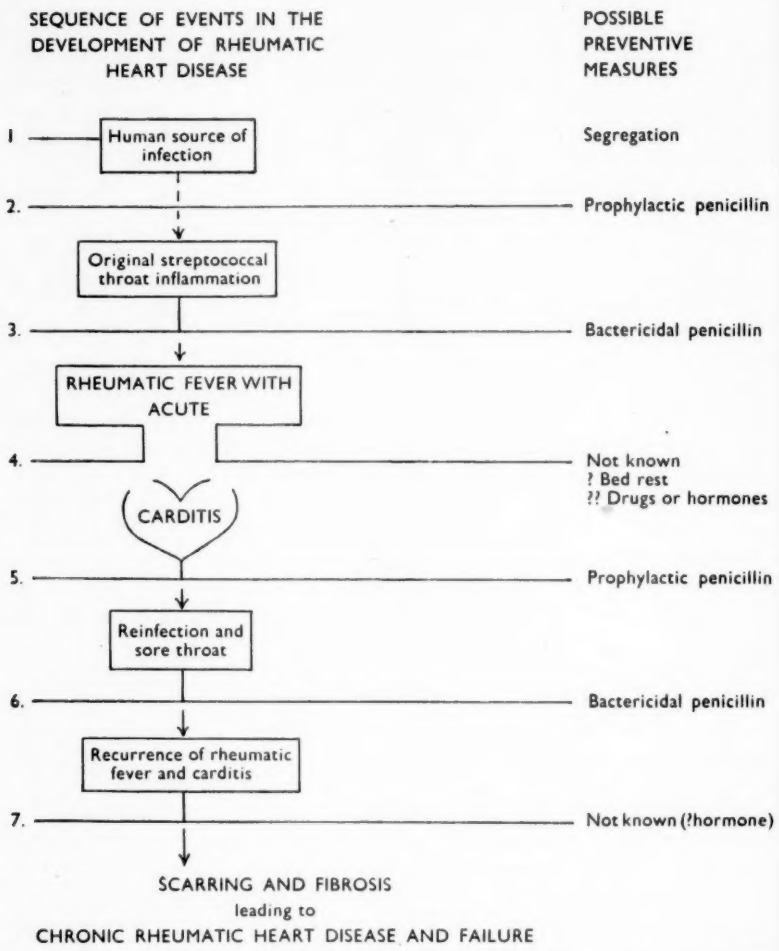

FIG. 1.—Diagram showing sequence of events in the development of rheumatic heart disease.

limits (e.g. Enticknap, 1953; McKeown, 1953). Such residual granulomas may be responsible for the maintenance of active fibrosis, since there is some evidence in other fields that progressive fibrosis depends upon

continuing inflammatory insults, e.g. silicosis. If these granulomas could be suppressed, on this theory, the valvular deformities might be halted. Whilst cortisone will decrease, and even in high dosage abolish, many inflammatory responses, we do not yet know what its effect is on the Aschoff body. Robles Gil, Rodriguez and Ibarra (1955) showed that there was reduction in the proportion showing active Aschoff bodies in patients treated with cortisone before operation. The numbers, however, were somewhat small. If these granulomas could be abolished by hormone treatment, it would still remain to be seen whether this might be done by a dosage which is safe enough to give over a number of years, and then whether subsequent valvular deformity could be prevented. In other types of fibrosis, such as that produced in the liver following toxic agents such as carbon tetrachloride, although cortisone decreases the initial fibrosis there is no difference after a period of months from those changes seen in the liver in untreated animals (Aterman, 1954).

The second possibility that mitral stenosis is due to surface accretion of fibrin, provides an even more difficult prophylactic problem. It is difficult to see how such a process could be prevented except by adequate healing of the underlying endothelial abnormality responsible for the accretion. Finally, of course, it must be remembered that a certain number of patients found to have rheumatic heart disease can give no history indicative of previous acute rheumatism, and in such the cardiac lesion is obviously not preventable.

BED REST AND THE PREVENTION OF CARDIAC DAMAGE IN AN ATTACK OF RHEUMATIC FEVER

Whilst only a proportion of children with rheumatic fever show cardiac involvement during the acute stage of the disease (72 per cent. of the children seen at Taplow) and only a small proportion of these are left with residual cardiac damage, so far as can be determined by clinical, electrocardiographic and radiological methods, we do not know what determines the localization of the process in the heart, or its severity. Further, we do not know how to prevent cardiac damage in the acute attack, although almost everyone believes that bed rest during the acute stage of the disease minimizes the residual cardiac damage. On theoretical grounds this seems possible, since bed rest reduces the total energy expenditure of children by about one-third, and the amount of trauma must depend largely upon the cardiac output, which again depends on energy expenditure. This measure was introduced first by Sibson in 1877, one year after the second edition of Hilton's classic work on 'Rest and Pain'. Sibson claimed that residual valve lesions were found in only one-eighth of patients treated by bed rest, as against one-third of patients who had not been so rested. Since that time, all who have treated rheumatic fever have stipulated prolonged bed rest, since there is no evidence that it does any harm (in the young, at least) and reasonable grounds for thinking it might do some good. The further decrease of cardiac output by

sedation is another possibility which we are anxious to explore. At the moment, it would seem to be wrong not to treat patients with acute rheumatic fever by prolonged rest, and we cannot therefore collect data concerning a control group treated without bed rest. In 1941, however, a study was made by Taussig and Goldberg, with a group of rheumatic fever patients who refused to remain in bed during the acute attack. Comparing this with a larger group of patients treated adequately with prolonged bed rest, they found that both the mortality and the proportion with residual valve lesions were much higher in the non-rested group. This is suggestive evidence for bed rest, but it is not conclusive since other factors may have been involved.

In our present state of knowledge therefore, bed rest is a most important mode of trying to minimize damage to the heart during the acute attack. We employ a series of graded stages at Taplow. In the first stage complete rest is obligatory: the child is not allowed to feed himself but is fed by a nurse. In stage two the child is allowed to feed himself and in stage three he is allowed to move around in the bed. The subsequent stages allow gradual mobilization and resumption of normal activity. We maintain bed rest at stage three for at least one month after the sedimentation rate (Westergren method) becomes normal, and somewhat longer if there has been any major degree of cardiac involvement. In some circumstances, for example heart failure (Wood, 1936; Payne and Schlesinger, 1935), the erythrocyte sedimentation rate is of little value since it may be within normal limits despite rheumatic activity. In such circumstances C-reactive protein estimations are often of value as an ancillary test. Mobilization should always be closely watched, and should evidence of a relapse occur, judged clinically or witnessed by a rise in temperature or sedimentation rate, the patient is put back for a further period of bed rest.

Recent work on the increase in metabolism due to salicylates might lead one to think that in the absence of fever, and in so far as cardiac output is concerned, bed rest alone is indicated. Abolition of fever by salicylates, however, would obviously tend to reduce cardiac output.

HORMONE TREATMENT AND THE PREVENTION OF CARDIAC DAMAGE DURING THE ACUTE STAGE

With the introduction of cortisone and corticotrophin in 1948, the hope was raised that carditis would be allayed and resultant cardiac damage decreased. Claims have been made that this is so (Wilson *et al.*, 1953), but most authors have felt somewhat disappointed with the results of hormone treatment. A joint cooperative study in the United States and the United Kingdom (1955) at 12 centres found little difference as regards cardiac status one year after the completion of treatment, between groups treated for six weeks with cortisone, corticotrophin and aspirin. Since that time some authors have made claims for different dosages or combinations of drug, but Illingworth's is almost the only controlled study (Illingworth *et al.*, 1957). He found that the

cardiac status at one year was better in those treated with cortisone and salicylate than with either alone.

Regardless of this important controversy, both hormones and salicylates are of value in certain circumstances in the acute stage. In the very mild case, bed rest alone is sufficient, but in cases with fever or joint pains which do not settle rapidly with bed rest and analgesics such as codeine, the good effect of salicylate has long been known. The cortisone group of steroids behave in a very similar way. Fever can be rapidly controlled and joint manifestations also subside within one or two days. Calcium aspirin is usually prescribed in a dosage to give a blood level above 20 mg. per 100 ml. of plasma, with a total daily dosage of say 30 to 60 mg. per lb. (65 to 130 mg. per kg.) body weight. Enteric-coated aspirin may be used if there is gastro-intestinal upset due to the irritant action of aspirin or calcium aspirin on the stomach, but this is rare with the latter. Hormone may be used in a similar way: a dosage of about 100 mg. of cortisone daily gives a reasonable suppressive effect but should be decreased after about four weeks. Treatment usually needs to be continued for a period of at least six weeks with gradual diminution of dosage during the last week. Some patients, however, relapse after cessation of drug administration and need further periods of treatment. With carditis of any severity, prednisone is more useful than cortisone or corticotrophin because it lacks salt-retaining properties. A daily dosage of 25 mg. a day, reducing later to 20 and 15 mg. according to clinical response and the sedimentation rate, is a satisfactory mean dosage level. All these patients should be on a daily prophylactic dosage of penicillin or sulphonamide.

We have had little trouble from hormone administration for such comparatively short periods as those needed in rheumatic fever; but, particularly in older patients, prednisone should be given after meals on a full stomach with aluminium hydroxide or other alkali in an attempt to decrease the incidence of gastric irritation. Hormones should be stopped if psychosis develops, usually with rapid return to normality. Other complications, such as supervening infection, seem to be rare, but if they do ensue it is important that the hormone dosage should not be decreased: if anything it needs an increase during the acute fulminating stage until antibiotics have taken effect. Rheumatic pneumonia is only seen rarely nowadays and usually in association with severe carditis. We have felt that salicylates can sometimes contribute to this state: if they are being given and rheumatic pneumonia or œdema develops, administration should be stopped and the patients changed to prednisone. Even this, however, is sometimes ineffective.

THE PREVENTION OF RHEUMATIC FEVER RECURRENCES

Once a child has had rheumatic fever, it should be realized that he is liable to recurrences and that, with each further recurrence, more residual heart damage is likely. We have shown that, over a period of years, the cardiac

status deteriorates in about one-fifth of patients with two or more attacks as against one in 100 of those who have only had one attack (Bywaters and Thomas, unpublished data). The prevention of further recurrences depends upon the recognition that every attack of rheumatic fever, as well as every recurrence, is set off by an attack of group A β-hæmolytic streptococcal throat infection: if these infections, to which we are liable from time to time, can be avoided, the child will suffer no further recurrences or associated worsening of the residual cardiac state. A small daily dose of sulphonamide or penicillin will effectively prevent the lodgement in, and invasion of, the tissues by group A streptococci. This principle of prophylaxis was introduced by Coburn and Moore and Thomas and France in 1939, and since then there have been many publications in the United States confirming their findings. In this country we have recently been able to show that the annual incidence of recurrences can be decreased by 80 per cent. (Bywaters and Thomas, 1958). The bacteria are transmitted mostly by manual contact and epidemics of scarlatina or hæmolytic streptococcal sore throat, without skin manifestations, occur particularly under conditions of overcrowding in the home, at school or in barracks. Unless a known rheumatic child is protected in this way, he is almost certain within a period of years to develop a recurrence of rheumatic fever. These epidemics usually occur in the colder months of the year but sporadic infection is always present, and we believe that protection should be conferred on these children all the year round at least until they reach adult life, when the opportunities for infection become somewhat less.

It is surprising that the routine protection of rheumatic children in this country should lag so far behind that in the United States, where during the last twenty years it has been universally accepted. In this country it is practised in only a few centres; there are only a few consultants or general practitioners at this moment who employ what is now a proven measure of prevention. The reasons for this have recently been surveyed (Bywaters, Hallidie-Smith and Thomas, 1957).

Sometimes objection has been made by the physician on account of cost, although a daily cost of between 2*d*. and 4*d*. seems a small price to pay for protection against a second attack of rheumatic fever and possibly further cardiac damage, cardiac invalidity and early death from rheumatic heart disease. Recent figures show that in the notifying areas of England, 0.027 per cent. of school children are attacked by rheumatic fever each year (Leff 1956). This figure was very much greater in the past and leaves every year its legacy of damaged hearts and liability to further recurrences. The proportion is therefore cumulative each year, and if the above rate applies to all the children of England and Wales, one can calculate that each year about 2000 children develop rheumatic fever and each of these needs protection for an average period of five years. The cost of protection is small compared with the cost of rheumatic heart disease and its treatment.

Toxic reactions with oral penicillin are very rare on prophylactic dosage

except when previous penicillin treatment has induced sensitivity or if there is a history of allergy. Reactions are mainly urticarial and mild, but shock and collapse have been described after one tablet (Dales, 1957). Before starting patients on prophylactic oral penicillin, a careful history should always be taken regarding previous allergy or penicillin reactions. In this small dosage sulphonamides seldom give rise to toxic reactions and in a five-year period at Taplow, with nearly 500 patients on prophylaxis, we have had only one serious reaction (agranulocytosis developing after eight weeks but recovering with antibiotic treatment). These few reactions usually occur within two or three months of starting treatment: i.e. usually while still under consultant care and before they have returned home. Streptococcal resistance to penicillin does not occur and only under epidemic conditions in closely crowded institutions has sulphonamide resistance appeared. Staphylococcal resistance to penicillin may be a nuisance but is unlikely to cause trouble under home conditions. We have had no trouble on this score. If a penicillin-resistant staphylococcal infection should occur in one of these patients, other antibiotics are available.

In practice, when the cooperation of the family doctor has been secured, lapses of prophylaxis such as have resulted in the few recurrences we have had in the protected group have usually been found to be due to parental factors: most parents when they have had the reasons for this tablet-taking fully explained cooperate well, but the degree of cooperation depends upon their capacity to understand and their conscientiousness and ability to supervise this measure in their children. Some recurrences we have had within the protected group have been due to practical difficulties, such as obtaining a renewed supply of tablets, and sometimes to the inability of the parent to understand its value after full explanation. Despite these difficulties it is quite possible to cut the rate of recurrences very considerably. In the United States, recurrences seem to be rather more frequent in the hospital-treated population—e.g. 13.7 per cent. (Rosenberg and Hench, 1946), 25 per cent. (Wilson and Lubschez, 1944), and a greater percentage decrease in recurrences with prophylaxis has therefore been attained. Even in this country, where recurrences in an unprotected group average something like 5 per cent. per year, this may be cut to about 1 per cent. The essence of this problem seems to be education both of the medical profession and of the parents of these children who have had rheumatic fever.

At the same time it should also be emphasized that subacute bacterial endocarditis occurring on the basis of old rheumatic endocarditis may sometimes be seen in childhood as well as in later life, and that this can also be avoided by preventive administration of penicillin or other antibiotic to cover such operations on infected foci in the upper respiratory tract as tonsillectomy and teeth extraction. All the above recommendations have been embodied in a report by the rheumatic fever committee of the Royal College of Physicians (1957) which is available on request to the College.

PREVENTION OF RHEUMATIC FEVER BY THE TREATMENT OF ESTABLISHED STREPTOCOCCAL INFECTION

Although we do not understand how an upper respiratory streptococcal infection produces rheumatic fever, we suspect that it has something to do with the development of immunity, since there is usually a period of a few days between the onset of a sore throat and the initial symptoms of rheumatic fever attack—the so-called 'silent period'. This applies both to the initial attack of rheumatic fever and to subsequent recurrences. When sulphonamides were first introduced, it was found that initial treatment of the sore throat failed to prevent the subsequent development of rheumatic fever (Coburn and Moore, 1939). Penicillin, however, is bactericidal for group A β-hæmolytic streptococci, whereas sulphonamides are merely bacteriostatic: when given in adequate dosage to a patient with a hæmolytic streptococcal sore throat, penicillin kills the organism and halts the infection, suppressing also the formation and liberation of antigen. In treated patients the normal antibody response to the infection is found to be diminished or absent, even when there has been a lag of up to five days from the onset of the sore throat in starting treatment (Brock and Seigal, 1953). In 1948, Massell *et al.* and Loge and Kilbourne showed that rheumatic fever was also preventable by this method and their results have been confirmed on a larger scale by Denny *et al.* (1950). The dosage of penicillin necessary for this bactericidal effect is crystalline penicillin G, 300,000 units four times a day for a total period of ten days. Alternatively, one intramuscular injection may be given using the long-acting benzathine penicillin, 1.2 mega units. (Penicillin appears to have no effect in established rheumatic fever.)

This method of rheumatic fever prevention, however, cannot be relied upon in the same way as the prophylactic daily administration of penicillin previously described, since, unless both parents and doctor are unusually vigilant, a proportion of such infections will remain unnoticed or the parent may even feel that the cold is too trivial to need the attendance of a doctor. The method, however, should be used whenever there is good evidence for the hæmolytic streptococcal origin of sore throat in patients with previous rheumatic fever or rheumatic heart disease, whether or not they are supposed to be on daily prophylaxis. Because of the difficulty sometimes encountered in distinguishing on clinical grounds between infections due to hæmolytic streptococci and those due to other organisms such as viruses, it will be inevitable that without bacteriological control some virus sore throats will be so treated. Although this can do little harm, it is probably best to await a throat-swab report, if this can be obtained within twenty-four hours and if the child has been seen within a day or two of the onset of the sore throat. Should neither of these conditions pertain, treatment should be given without reference to bacteriological indications. In children who have not had rheumatic fever, and in whom there is no family history of such, this is the only method of preventing first attacks of rheumatic fever since no-one would advocate the universal use of daily prophylaxis.

THE PREVENTION OF FIRST ATTACKS OF RHEUMATIC FEVER

Rheumatic fever is decreasing in incidence and in severity in this country and in others where there is a high general standard of living, but is still rife in overcrowded slums. It is particularly important to use the method of prevention which I have described (using immediate and adequate bactericidal penicillin) in anyone giving a family history of rheumatic fever or rheumatic heart disease, who is living under such conditions or mixing for the first time, as at school or training camp, with large numbers of other young adults. In such institutions watch should be kept for epidemics of streptococcal infection, since many cases of rheumatic fever may be prevented by bringing the epidemic under control as soon as possible—using universal prophylaxis.

With such specific measures and with the general improvement in housing and hygiene which this century is witnessing, rheumatic heart disease should become one of the rarer instead of one of the most common cardiac conditions of young adult life.

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THE TREATMENT OF GOUT

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In discussing treatment it is a good discipline to see how this marries with our conception of etiology. Gout is due to an abnormality of purine metabolism, partly hereditary and probably due to a fundamental abnormality in the metabolism of the nucleotides (Wyngaarden, 1957). It is associated with the deposition of urates in the tissues and often with a raised plasma uric acid over which there may be some endocrine control—witness the lower uricæmia and rarity of attacks in women before the menopause. As Hippocrates pointed out many years ago (Sydenham Society, 1849) 'Eunuchs do not take gout. A woman does not take gout unless her menses be stopped'. The attacks may be triggered off by stress, often specific for the individual.

THE IMPORTANCE OF THE HISTORY

In gout a careful history often pays a good dividend. Worry, trauma, fatigue, cold, infection and idiosyncrasies to certain foods or drink may be important trigger factors and the same type of stress may always be the important one in a particular case. One patient may only get attacks when worried or excited, another when he twists or injures a joint and another only on eating or drinking some substance quite innocuous to the ordinary individual. One man's meat is another man's poison. In this connexion it should be remembered that it is not the alcohol content that matters but its vehicle. A wine-glass of cyder may prove more dangerous than a whole bottle of gin. Champagne, heavy wines and beers, however, have a bad reputation, as have rhubarb and strawberries. A late night with good food and plenty of wine, coupled with the excitement that may follow, is particularly lethal. Surgery as a form of trauma may well precede an attack and calls for anticipatory suppressive treatment. Infection is often forgotten when a diagnosis of gout has been made. It may certainly precipitate an attack and in many cases sepsis may be the cause of prolongation and increased frequency of attacks to such an extent that the original diagnosis may be called in question. Avoidance of particular stresses to which the patient happens to be susceptible is an important part of treatment.

Treatment falls automatically into two main categories: that necessary between, and that required during, the acute phases. To be successful, interval treatment must be continued indefinitely, the acute treatment being superimposed on this when necessary. Drugs used for long-term treatment may accentuate the attack rate for the first six weeks and, with this in mind,

maintenance dosage of acute-phase drugs may be advisable during this period.

INTERVAL TREATMENT

Certain foods and drink rich in purines and nucleoproteins are best avoided or taken in moderation only—sweetbreads, fish roes, herrings, sardines, anchovies, offal and meat extracts and perhaps coffee—but less stress is placed on this type of dietetic restriction these days. Fatty foods should also be restricted and in general an 'aldermanic' diet is most unsuitable. It was interesting to see how many people had their first attacks of gout after the austerity of the war when they visited the United States or Switzerland. Plenty of fluids, attention to the bowels and regular exercise, but not unaccustomed exertion, are advisable. Sweating treatments are often helpful: the vapour bath or Turkish bath, with the proviso that it is not followed by any rough massage or manipulation—the latter is an excellent way of provoking an attack.

Apart from the avoidance of stresses, the uricosuric drugs hold pride of place in interval treatment. Until recently physicians have fallen into two camps in their preferences: aspirin or probenecid, but recently certain phenylbutazone analogues have entered the arena and are proving formidable competitors. The uricosuric drugs appear to act by reducing resorption of uric acid by the tubules from the glomerular filtrate of the kidneys. They have no benficial effect on the acute attacks *per se*, but the increased uric acid excretion is followed by a reduced plasma uric acid level and later by reduced frequency and severity of attacks, with eventually actual reduction in size and softening of tophi. These latter benefits make themselves manifest after some six weeks. In any patient who is having frequent attacks of gout, or in whom tophi are forming, the use of these drugs has proved a great advance in treatment. When attacks occur only infrequently their value is of course problematical, but some lead may be obtained from the degree of hyperuricæmia. To avoid deposition of urate in the urinary tract, it is important to give plenty of fluids and prevent the urine becoming strongly acid during uricosuric treatment.

Salicylates and *aspirin* were first discovered to be uricosuric agents by Jennings in 1937, but Marson (1953) has refreshed our memory on the subject and added much further information. To be effective, salicylates or aspirin must be used in large doses and, like all these drugs, must be continued for years or indefinitely: 60 to 140 grains (4 to 9.3 g.) of salicylate should be given in the twenty-four hours and this is sufficient to cause gastric disturbance in many patients and even hæmatemesis. In many other cases there will be some depression and often tinnitus. These latter symptoms tend to become less after some weeks of treatment. If, however, aspirin or salicylates are tolerated, they are very effective and also cheap.

In 1951, *probenecid* followed caronamide as an agent for increasing blood penicillin values, but was rapidly added to the therapeutic armoury for gout.

It is best to start with a dose of 0.5 g. daily and, if well tolerated, increase by weekly increments to 1.5 or 2 g. It is well tolerated by about 80 per cent. of patients, but 8 per cent. will get gastric disturbances and 5 per cent. a rash. (Gutman and Yü, 1957.) During the first six weeks there may be an increase in the number of attacks; hence colchicine, 0.5 mg. three times a day, is advised during this period. Aspirin or salicylates should not be given at the same time as this reduces the uricosuric effect. For the patient who tolerates probenecid well, it has certainly been, until recently, the drug of choice: only 2 to 4 tablets a day are necessary and there are then no depressive or other undesirable effects. While it is being taken, however, some care is necessary in using other drugs, for instance large doses of bromide, as their excretion may be delayed, with consequent toxæmia.

Recently, *phenylbutazone analogues* have proved very potent in promoting uric acid excretion. Phenylbutazone is mainly antiphlogistic but slightly uricosuric. Many compounds akin to phenylbutazone have been tested for both these properties and it seems that the more acid of the series become less antiphlogistic, less toxic but more uricosuric. Such a compound, G.28.315 (Geigy), has recently been assessed, and in a dosage of 400 mg. four times a day—it is rapidly absorbed and excreted—it appears to be more potent than probenecid 1.5 g. daily, and, in a four-month trial in 16 cases, has proved completely non-toxic (Kersley *et al.*, 1958). Ogryzlo and Harrison (1957) suggest that 3 grammes of probenecid, 6 grammes of aspirin, 1 gramme of phenylbutazone and 0.5 gramme of G.28.315 have approximately the same uricosuric effect but, of course, phenylbutazone is ruled out at once for long-term usage in this dosage because of its toxicity.

We (Kersley *et al.*, 1958) found the average increased excretion of uric acid in the urine to be from 551 to 880 mg. a day on giving 100 mg. of G.28.315 four times daily and to 1,042 mg. on double this dosage. On 400 mg. daily the plasma uric acid fell from 7.8 to 4 mg. per cent. This was a significantly greater fall than with 1.5 g. of probenecid (to 5.2 mg. per cent.) and the excretion with probenecid was again less. Intermittent treatment with G.28.315, as was the practice with cinchophen ('atophan'), was not satisfactory as, within four days of stopping the drug, the plasma uric acid returned to its previous high level. Giving aspirin at the same time as G.28.315 abolished its uricosuric effect and even 0.7 g. greatly depressed uric-acid excretion. A definite tendency to increased attacks of gout was noted in the first month of treatment, but after this they became less frequent and less severe if not ceasing entirely. Chronic stiffness and swelling, when present, also tended to disappear.

Steroids have been tried for their uricosuric effect but their use is not justified, as dosage must be high and continued. Another drug, *p*-carboxy benzal sulpho-diethylamide, allied to probenecid, is under trial, but so far it does not appear to have any advantage over G.28.315.

THE ACUTE ATTACK

For the acute attack of gout the treatment can be divided into local and general. The joint must be protected and is usually best kept warm, though a few sufferers prefer cold applications and evaporating lotions. Soaking in

a hot hypertonic solution of magnesium sulphate, hot compresses of this nature and lightly binding in hot wool are advisable. Mud packs may be very soothing and in the later stages, when the most acute phase is over and if resolution is delayed, contrast bathing or gentle douching and very gentle massage and movement coupled with a sweating regimen will hasten recovery.

Two drugs are of great importance in the treatment of the acute attack and vie with each other for popularity: colchicine and phenylbutazone. The former is time-honoured and is effective in about 90 per cent. of cases provided the dose given is sufficient. It has no effect on other rheumatic conditions and is therefore sometimes used as a therapeutic test for gout: $\frac{1}{120}$ grain (0.5 mg.) is given two-hourly until the acute attack starts to subside or nausea or diarrhœa occurs. The colchicine is then stopped for twelve hours and restarted, two or three times a day, after this interval. Demecolcine has been claimed to be equally effective and to have less gastric irritant effect (Neustadt, 1958). One milligram may be given hourly until some relief of symptoms or an irritant effect is produced.

The rival treatment, which is becoming more and more popular and is effective when colchicine fails, is the use of 600 to 1000 mg. of phenylbutazone for two days only. Given for this short period no complications have so far been recorded and it seems always to be effective. Colchicine, however, should replace phenylbutazone for suppressive interval treatment.

Corticotrophin has been advocated for the acute attack but it will be followed by a rebound attack three or four days later unless followed by adequate colchicinization and it has little to recommend it, compared with phenylbutazone which can also, of course, be given by injection.

SUMMARY

The treatment of gout between attacks consists in a general regimen of reasonable temperance in food, drink and exercise and the elimination of certain stress factors, at the same time giving one of the uricosuric agents: salicylates, probenecid or G.28.315. Suppressive colchicine administration is advisable for the first four to six weeks.

In the acute attack protection of the joint and the use of colchicine in full dosage, or phenylbutazone in large dosage for two to three days only, are indicated.

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PHYSICAL TREATMENT IN CHRONIC RHEUMATISM

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The chronic rheumatic diseases are characterized by similar symptoms and disabilities in the locomotor system—pain, stiffness and limited movement, muscular weakness and progressive deformity. In the absence of any drug or treatment which cures the disease, physical therapy plays an important part in treating the symptoms and disabilities of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Localized soft-tissue lesions such as bursitis, frozen shoulder and fibrositis will not be discussed.

A major advance in physical medicine in the last decade has been the recognition of the limitations of passive physical methods in treating the chronic rheumatic diseases, and the value of controlled, carefully prescribed active exercise. Another major advance has been to recognize that physical therapy is not an alternative or competitive treatment to medicine or surgery, but part of it, and cannot be considered in isolation. This is particularly important when such potent drugs as the steroids are in use as they modify symptoms and mask underlying lesions.

The majority of subjects with rheumatic diseases do not need hospital attention. Aspirin for pain relief and simple home physical treatment such as rubefacients and hot-water bottles may be adequate. The patients most severely affected by rheumatoid arthritis and ankylosing spondylitis need inpatient hospital treatment. As they are suffering from constitutional illnesses and tire easily a programme of physical treatment necessary to deal with the many problems involved may well be too exhausting for the patient. Frequent short periods of treatment, with rest intervals, are more valuable than long treatment periods two or three times a week. So far as possible, outpatient physical treatment should be avoided for these patients, particularly in winter. Patients with osteoarthritis are usually in good general health and tolerate outpatient treatment well, but again the old and frail need careful consideration before attendance as a hospital outpatient for physiotherapy is prescribed. In fact, although osteoarthritis is the commonest condition treated by physiotherapy in hospital outpatient departments, the proportion of these subjects who really need and derive benefit from physiotherapy is unknown. The acute painful episodes occurring in joints in primary generalized osteoarthritis are self-limiting. Reassurance that the patient has not rheumatoid arthritis, analgesics and home remedies are usually sufficient. In degenerative joints physical treatment does not affect the pathological process and, with the exception of exercise to stabilize

and control joints and to improve posture, is entirely symptomatic.

RELIEF OF PAIN

Almost any source of *heat* may be used for pain relief: hot-water bottles, electric blankets or pads and hot baths are almost as valuable as the specialized equipment found in hospital, but infra-red radiators and luminous heat lamps are more convenient to use, can be better controlled and more accurately directed. Short-wave diathermy, although commonly prescribed, has little advantage over superficial heating in rheumatoid arthritis except for the hip and shoulder. If used on other joints at an active stage of the disease, pain is often increased. Paraffin wax baths, using paraffin wax at its melting point (115° to 120°F. [46° to 49°C.]) or hot-water baths at 106° to 110°F. (41° to 43°C.) are convenient ways of relieving pain in the hands and feet. When many joints are involved general hot baths with temperature progressing from 98° to 105°F. (37° to 40°C.) are useful. Moist heat, as mud or peat packs at temperatures of 115° to 120°F. (46° to 49°C.) are used as hot compresses, mainly for hot swollen knees and ankles. For home therapy they can be replaced by hot poultices or hot moist towels. In the active rheumatoid joint counter-irritation is more effective than heat in giving lasting pain relief. It is given as a controlled burn with the Kromayer ultra-violet lamp, or with the cautery. Dosage should be carefully prescribed. Second- or third-degree erythema doses to several areas at intervals of a few days are better tolerated than fourth-degree erythema doses at longer intervals. When the joint is painful, but without much effusion, diathermy may be used.

It must be emphasized that the primary treatment of a painful active joint is *rest*, not physical therapy. So far as is known no form of physical treatment really affects the disease process in the joint. Rest offers protection for the weight-bearing joints during the active stages of the disease, and methods which may relieve pain and allow use of these joints may allow damage to continue unhindered and are not, in the long run, in the patient's interest. In the non-weight-bearing joints intra-articular injections of hydrocortisone can be given at an early stage with real advantage. When hydrocortisone injections are used in the lower limbs to control pain and swelling, the symptomatic relief must not be allowed to influence the time at which weight bearing is allowed. The use of hydrocortisone locally into joints and tendon sheaths has considerably altered physical treatment of the upper limbs in rheumatoid arthritis.

In *osteoarthritis* superficial heating is rarely valuable in pain relief, except for secondary stiffness, and either deep heating (short-wave diathermy, or ultra-sound) or counter-irritation is indicated. For the hip, deep heating usually gives some relief. The knee is conventionally treated with diathermy, but controlled trials (Simpson, 1956) show that counter-irritation gives better clinical results. A possible reason for this is that osteoarthritis of the knee is often accompanied by painful fat-pads around the knee, and these

respond well to counter-irritation. Ultra-sound has no advantage over diathermy in treating osteoarthritis. In osteoarthritis of the spine, muscle spasm and pain are relieved by any form of heat; we prefer to use short-wave diathermy. Pain from the spine and hip in osteoarthritis may be due to capsular contractures, for which stretching or manipulation under anæsthesia may be indicated. Hot baths may be used to the level of tolerance for widespread degenerative joint disease: painful muscle spasm is relieved, the muscles relax and increased joint movement is possible, helped by the support given by the water.

Physical methods often fail to relieve pain in osteoarthritis because of poor prescribing. The duration and frequency of treatment are often inadequate. Thus, not uncommonly heat treatment is given for twenty minutes, two or three times a week—for the convenience of a busy physiotherapy department and of the patient. If a course of treatment is to be drawn out over many months, this may be justified, but the aim of the treatment—pain relief—should be kept in mind. A short intensive course, for example, thirty to forty minutes of diathermy once or twice a day, for ten to fourteen days, combined with appropriate exercise, will often prove effective.

In *ankylosing spondylitis* pain is usually relieved by deep x-ray therapy (Sharp and Easson 1954), but it may be contraindicated: e.g. in a young woman. For pain and muscle spasm of the back and major joints relaxation in warm water (98° to 102°F. [37° to 39°C.]), combined with simple movements, is indicated. Spinal, paravertebral, or costal pain can be treated by counter-irritation, and massage with the moving head of the Kromayer lamp, to produce a second- or third-degree erythema, is convenient and effective. For sharply localized bony and periosteal pain which occurs round the trochanter, iliac crest, ischial tuberosity and heels, ultra-sound, using a stationary or slow stroking technique and a high output (2 to 3 watts per square cm.) is very effective.

RELIEF OF STIFFNESS

Heat, massage, controlled exercise and hydrotherapy may all be used to relieve spasm and stiffness. The rheumatic diseases are characterized by morning stiffness, and a preliminary 'warm-up' first thing in the morning with a heat cradle followed by simple rhythmic, free swinging exercises is valuable. Morning stiffness is very resistant to drugs (other than the corticosteroids), even when good pain relief has been obtained.

Relaxation in the deep warm pool (98°F. [37°C.]) is helpful, and the ankylosing spondylitic will show a measurable improvement in posture and a gain in height (Harris, 1958). Massage baths, with the patient either massaged by hand, douche or spray of hot water, relieves muscle stiffness, but is too tiring for the patient with active rheumatoid arthritis. The general muscle stiffness and 'fibrositis' which sometimes follow rheumatic fever respond well to massage baths.

If hydrotherapy is not available, light stroking massage following pre-

liminary superficial heating is soothing and relaxes spastic muscle. In osteoarthritis in particular, this relief is short-lived. Massage should be used with caution—it is a potential 'drug of addiction'. Stiffness may also be relieved by repetitive movement, and occupational therapy, where carefully graded repetitive movements can be carried out for long periods without losing the patient's interest, is useful. Passive stretching of a joint and its surrounding muscle, when pain has been relieved by heat and local anæsthetics, or gentle mobilization under general anæsthesia, will usually increase the ease and freedom of movement of the joint and reduce its stiffness within the range, even if the total range of movement is not actually increased.

RESTORATION OF MOVEMENT

Controlled exercise, careful positioning, serial plaster splints, assisted movements following heat and exercise in warm water, all help to increase joint mobility. When movement is limited by pain and spasm, heating techniques and local rest are used; when weakness limits movement, muscle-building exercises are used; when stiffness limits movement, relaxation techniques are indicated. These may be combined in the deep pool, where relaxation and pain relief are produced by the hot water, which is also used to assist weak muscles and stiff joints, or to provide resisted exercise. Where hydrotherapy is not available or is contraindicated, a similar combination of support and resistance and relaxation can be produced on the Guthrie-Smith apparatus with springs and slings. Exercise in warm water is very exhausting. A rest period of at least thirty minutes is essential afterwards. We do not permit our patients with rheumatoid arthritis to take any active exercise in the following two hours. Limited movement is often combined with deformity. Careful positioning in relaxation is helpful: e.g. prone lying for the flexed hip or knee.

Prolonged immobilization of a joint is followed by permanent limitation of movement. This takes place rapidly in ankylosing spondylitis and Still's disease but the rheumatoid joint may be safely immobilized for several weeks. There is no advantage in attempting to put a painful inflamed joint through a daily range of passive movement as is often suggested. Muscle function should be maintained by static contractions within the plaster. The plaster should be split when pain has settled (usually 7 to 10 days) and assisted movements be carried out daily, preferably in the deep pool.

In ankylosing spondylitis the thoracic cage is stiff and chest excursion may only be one or two centimetres. Breathing and postural exercises must be given and the patient instructed in their home use. Chest movement can be helped by arm and shoulder movements. Skilled and enthusiastic instruction is essential. The patient must be warned of the absolute necessity of keeping up his exercises, and he should be periodically checked in his performance of them. In osteoarthritis of the cervical spine, movement of the neck will usually increase after wearing a felt, cardboard or plaster collar for some weeks, or alternatively giving local heat and head traction.

Occupational therapy, carefully planned so that the particular movement required is carried out repeatedly over an increasing range, will not only increase range of movement, but increase ease and power of movement within the given range. For example, a treadle fret-saw will give repetitive knee movements, or a loom with an overhead beater will give shoulder extension and flexion exercise. In these instances load should be small but the total number of movements high. Movement may be limited by soft-tissue contracture or shortening, and these will not respond to exercise: manipulation under anæsthesia, or surgery will be indicated and save the patient and therapist months of unavailing work.

RESTORATION OF MUSCLE STRENGTH

Marked weakness and wasting occur in the muscles around and controlling painful joints. The only way to build up weak and wasted muscle is by exercise, which should be preceded by heat to relieve pain and spasm. A careful balance between rest and exercise is essential. Rest, like exercise, must be prescribed in detail. The patient should be provided with a detailed daily programme. In general, exercise periods should be followed by rest periods or passive treatments, and the most important group of exercises performed at the time of day when the patient is at his best. For the rheumatoid patient this is usually in the forenoon. The patient's morale and enthusiasm must be kept up. Team games and occupational therapy are extremely valuable for this. In rheumatoid arthritis where muscle is itself involved in the disease process, exercise must be given cautiously and not to the point of fatigue. Static muscle exercises are indicated initially and these can be given as 'muscle setting' without moving joints, and to muscles controlling joints which are resting in plaster. No controlled experimental work has been done on methods of building up strength of muscle in rheumatoid arthritis as has been done for normal muscle, muscle after injury and poliomyelitis (De Lorme, 1946), but our impression, based on the rehabilitation of more than a thousand patients with rheumatoid arthritis treated in the last five years, is that progressive resistance exercise is valuable. Low repetition against a submaximal load should be used, and the initial working load must be carefully assessed individually. It is usually about one-third of the single maximal lift, but will be found to vary from day to day, and is different at different times of the day. Highly skilled and specially trained physiotherapists and remedial gymnasts are needed for this work. Exercise against weights, through pulleys, is preferable to exercise against spring resistances. Locally fixed weights (e.g. a weighted boot) should be used with caution. In all systems careful stop or rest positions must be arranged so that the joint will not be subject to strains. Electrical stimulation is rarely needed. It is used only to re-educate the patient in the feel of muscle contraction, and does not replace active exercise. We have employed it in less than 2 per cent. of the last 1000 patients with chronic rheumatic diseases we have treated.

Although patients with ankylosing spondylitis when pain-free tolerate exercises well, their muscle is abnormally fatiguable, and they should not be worked to the fatigue point. A general postural exercise programme, concentrating on back extensors and respiratory muscles, is needed. On this, vital capacity and exercise tolerance increase. In osteoarthritis, although wasting and differential muscle weakness are found, the muscles themselves are not involved in the disease process. They can safely be given progressive resistance exercises, and work against maximal load.

In rheumatoid arthritis in particular, occupational therapy, where carefully graduated work can be organized under skilled supervision, is valuable for building up both general stamina and particular muscle groups. Work can be either general or specific and should be defined.

Exercise in water allows weak muscles to move through a physiological range and maintains the important lengthening and shortening activities of muscle. By limb positioning or the attachment of floats, weights or paddles, graduated muscle exercise can be given. Walking re-education can begin in the deep pool, as limbs which are too weak to take the full body weight will easily support it in water.

It is not generally appreciated that re-education of muscle is as important in rheumatoid arthritis as in poliomyelitis, and in practice it is much more difficult owing to the complications of pain, joint involvement and generalized disease. In degenerative disease of weight-bearing joints, probably the most useful preventive measure available is to strengthen the weak muscles to re-establish control over the joints and minimize further damage.

THE ACTIVE STAGE OF RHEUMATOID ARTHRITIS

In the active stage of the disease the principal symptoms are those of a general disease with joint and soft-tissue manifestations. The condition is potentially reversible. The main treatment is medical and consists of rest, both general and localized (i.e. rest plasters), and appropriate drugs. The only physical treatment necessary is general bed exercises to prevent loss of muscle tone, particularly in the postural muscles, to prevent deformity, to maintain joint mobility and to preserve cardio-respiratory efficiency. Superficial heat for painful joints may help to reduce drug dosage, or enable a less toxic drug to be used. Simple methods such as hot-water bottles or kaolin poultices are almost as useful as more expensive physiotherapy equipment. Massage and electrical treatment are not indicated. During this stage special attention should be given to the weight-bearing joints. Plantar flexion deformity of the ankles should be prevented with cradles or foot boards and any knee deformity corrected. As the feet are commonly involved, weight-bearing pain should be anticipated and minimized by suitable shoe alterations.

As the general condition improves and joints quieten down, exercises are gradually increased in duration, frequency and power. In the most active stage bed exercises are conducted for 5 to 10 minutes once or twice daily

and gradually increased later to 20 to 30 minutes twice a day. In general, hydrotherapy is not indicated in the acute stages but, as the condition quietens, walking instruction in the deep pool is valuable. No formal occupational therapy is indicated.

A high proportion of patients will recover, but some will progress to the subacute and chronic stages.

SUBACUTE AND CHRONIC STAGE OF RHEUMATOID ARTHRITIS

If general symptoms predominate, bed rest and exercise as in the acute stage are indicated, but if only a few, or single, joints are affected then local rest by plaster splintage is adequate. The treatment of the painful active joint in the upper limb has been greatly modified by the use of intra-articular injections of hydrocortisone. The painful elbow or wrist settle down rapidly with 0.5 to 1 ml. of hydrocortisone acetate in 1 to 4 ml. of 1 per cent. procaine. Pain and swelling are reduced and long-lasting benefit can be expected. Usually two injections a fortnight apart are adequate. For the wrist a light removable dorsal plaster cast is also used. This technique has almost completely superseded physical means of achieving pain relief for these particular joints. We do find occasional indications for intensive local counter-irritation for the wrist joint either by the Kromayer lamp (a second or third degree erythema dose twice a week) or with iontophoresis with silver nitrate (2 milliamperes for five minutes, two to three times a week).

For pain relief of the *shoulder* hydrocortisone in a larger volume of local anæsthetic (1 to 2 ml. of hydrocortisone in 8 to 10 ml. of 1 per cent. procaine) is injected widely around the capsule of the joint, into the capsule, the joint and the subdeltoid bursa and into the bicipital groove. This is combined with thirty minutes of diathermy daily, and free rhythmic shoulder exercises in the deep pool, or on springs. Until pain has been relieved vigorous exercise is impossible. Auto-assisted pulley exercises, and purposive exercises for the shoulder and whole upper limb, in classes, should follow. For the active *hand* adequate rest in plaster is desirable and this should be combined with physical treatment. In the tender, swollen, generally involved hand the treatment we consider of greatest value is citrate iontophoresis (Coyer, 1954). This is given as a hand bath of 1 per cent. potassium citrate, with a current of 5 to 10 milliamperes for twenty minutes daily or on alternate days. We have found this to give relief in more subjects than do paraffin wax baths and this is borne out by controlled trials. It may also give relief when wax has been tried unsuccessfully. Paraffin wax baths are easily adaptable for home use and, although in the acute stage they are of limited value (Harris and Millard, 1955), they are the most useful form of physical treatment available for the stiff, painful hand. Both these treatments are followed by finger exercises of a purposive type. Each joint must be deliberately and slowly moved through a full range of movement. Flexion is the most important movement, and hyperextension at the proximal interphalanged joint, a most crippling deformity, must be prevented. A skilled physio-

therapist is essential to give correct instruction and to provide manual traction when deformity is present.

Paraffin wax baths can be used at home as follows:—

For hands.—Put 4 lb. (2 kg.) of wax into a 7-lb. (3 kg.) jam jar. Put the jam jar into a saucepan of water and heat until the wax has melted. Do *not* continue heating after the wax has melted as it is now at the right temperature for use.

Immerse the hand in the jar for 30 to 45 minutes, exercising the hand by opening and closing it while in the wax.

Peel off wax and exercise by clenching or by squeezing a rubber ball or ball of wool for 5 to 10 minutes.

For feet.—Treat in similar way using an enamel or plastic basin instead of a jam jar.

Note.—Do not put the jar or basin containing wax directly over heat.

A simple alternative for frequent home use is 'hot gloving':—

Get a pair of heavy household rubber gloves. They must be completely waterproof, which is tested for by first filling the gloves with water. Rub oil of wintergreen ointment or 'iodex' on to the hands. Fill a bowl or jar with hot, not boiling, water. Put on the gloves. Put the gloved hands in the water taking care that water does not get into the glove at the wrist. Keep the gloved hands in the water for 10 minutes, take them out and remove the gloves. Exercise the hands by clenching the fist round a small rubber ball, and by doing the finger exercises you have been taught. Do this at least three times a day.

These treatments carried out at home avoid the strain of frequent attendance at hospital. They have the advantage of being used at the time of day the patient most needs them—usually in the morning. They are useful psychologically, as the patient feels he is taking an active part in treatment.

Where relatively few joints of the hand are involved and are particularly painful and swollen, hydrocortisone injections, 0.25 ml. of hydrocortisone acetate and 0.75 ml. of 1 per cent. procaine, are indicated, the joint having first been aspirated. Useful alternatives are strong counter-irritation with the cautery (Burt, 1958), ultra-violet light, or silver iontophoresis. A convenient electrode for this, made of 1 inch (2.5 cm.) diameter rubber tubing and packed with silver-nitrate-soaked cotton-wool, fits most small joints. Much hand disability is due to tendonitis and nodules in the flexor sheaths in the palm. These are often confused with capsular and ligamentous contractures and are unaffected by physical treatment. They usually clear up spontaneously, but immediate relief can be achieved by injecting small quantities of hydrocortisone and procaine into the flexor sheaths. Occupational therapy is invaluable in providing finger and hand exercise and in retraining in skilled deliberate movement.

In the *lower limbs* the most important factor in relief of pain is relief from weight bearing. Local injection of hydrocortisone will temporarily relieve pain in these joints, but may encourage injudicious weight bearing. This method of easing pain and controlling effusions of joints may be necessary, but should not be allowed to influence the programme of weight bearing. Plaster or plastic casts will help earlier weight bearing by preventing strain—they do not 'strengthen' the joint or replace muscle power. Weight bearing should not be allowed until the muscles have been sufficiently educated to

take the patient's weight, and she should progress from walking in the deep pool to walking with crutches, sticks, and then unaided. Weight-relieving calipers may be required.

Pain from the *hip joint* may be helped by deep heating with short-wave diathermy or ultra-sound. If these fail, counter-irritation may be tried. Physical treatment for rheumatoid hips with much structural change is not satisfactory. Limitation of weight bearing is indicated. Pain from the *knee joint* responds to counter-irritation but deep heating appears to be no more valuable than superficial heating. A painful knee joint is always accompanied by wasting and weakness of the thigh muscles, and careful rebuilding of these muscles is essential. In the most painful joint, only static exercise—muscle setting—which does not move the joint, is indicated, and this should be done slowly and strongly ten times every hour. These exercises can be done when the knee is in plaster. As pain decreases exercise is increased and progressive resistance exercises are instituted. Weight bearing is not permitted until the extended leg can be raised against gravity. If movement of the knee is limited, exercise in water or free exercise on slings and springs will assist recovery, as will occupational therapy. A stiff knee is a great handicap, but care must be taken not to turn a stiff painless joint into a painful one. Flexion deformity should be corrected by serial plasters, traction, manipulation under anæsthesia, or surgery.

Physical methods for relieving pain in the *ankle*, subtaloid and mid-tarsal joints are not very satisfactory, and rest in plaster or avoidance of weight bearing are the most important factors.

Wax baths, given by continuous immersion—that is, with the patient sitting with the feet immersed in a paraffin wax bath for a minimum period of 30 minutes daily—and followed by mobilizing exercises are helpful, but soften the feet. Gentle manipulation of the feet and toes should follow. The important movements are a 'wringing' action of the forefoot on the mid-tarsus, anterior-posterior movements of the metatarsal heads on each other, and stretching of the toes. This calls for a highly skilled physiotherapist as the foot may be mobilized, but made more painful. Simple shoe alterations (metatarsal bars, valgus stiffeners, flanged heels) are valuable. Occupational therapy is particularly useful in mobilizing the ankle joint, and foot-operated sewing machines, treadle fret-saws and similar apparatus can be adjusted to provide repetitive and progressive exercise.

The *cervical spine* is commonly involved in rheumatoid arthritis. Rest and relative immobilization in a collar are necessary if x-rays show instability. Pain can be helped by almost any form of heat. Inductothermy, with the coil wrapped round the neck, is the most useful. Segmental pains may be present, and may be confused with pains arising in other upper limb structures. A collar is indicated.

If many joints are painful and stiff and the muscles in spasm, a warm bath is helpful. In hospital, in the deep pool or tank, this can be combined with exercise and joint movement. At home a daily hot bath to the limits

of comfort should be taken and simple exercises performed. A regular daily exercise routine must be carried out, whether the patient is at home or in hospital. It consists of slow deliberate movements of each joint through its full range, breathing exercises, postural exercises, and 'muscle settings' of all anti-gravity muscles. Home exercises must be simple, and complicated exercise tables are rarely worth while. The patient's intelligence and personality must be taken into account when teaching a programme of home exercises. Unless they are easily remembered and only take a short time daily most patients soon abandon them. (Parker and Bender 1957.)

ADVANCED STAGE OF RHEUMATOID ARTHRITIS

In the advanced stages of the disease, when many joints are fixed and deformed, it is important to be realistic in the approach to the patient. Pain may be relieved by the methods previously described, but the greatest importance must be attached to functional retraining. Active physical exercises, preferably in groups, will build up muscle and morale. An attempt should be made to mobilize joints and, for the shoulder joint in particular, gentle mobilization under anæsthesia is valuable. The 'activities of daily living'—dressing, washing, feeding and toilet activities—are taught in the occupational therapy department. Rehabilitation and resettlement are beyond the scope of this article.

ANKYLOSING SPONDYLITIS AND GOUT

In addition to the measures discussed, it is necessary to instruct the patient in a regime of exercises to be carried out regularly at home. These must be simple, and take no more than ten minutes twice a day, otherwise the patient will not continue with them. The exercises should concentrate on maintaining chest mobility, preventing deformity and strengthening postural muscles. These should be combined with instructions in daily prone and supine lying on a hard surface (the floor) and the use of a hard mattress. The patient attends the hospital until instructed and should be checked through his exercises at two months and one year.

Gout.—Gouty joints are relieved by moist heat. Hot steam baths are particularly useful, as no pressure is applied to the painful joint. Detailed treatment is discussed elsewhere.

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THE DIFFERENTIAL DIAGNOSIS OF RHEUMATISM

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RHEUMATISM is a meaningless if convenient term for diverse conditions; its boundaries are imprecise, and attempts at classification founder between the descriptive and the etiological. Furthermore, the 'splitters' recognize subdivisions unacceptable to the 'lumpers', so that the tendency to terminological confusion persists. There are, however, certain terms which most rheumatologists of today regard as obsolete. These are bracketed in the following simplified classification of the commoner arthritides:—

(1) Rheumatic fever

(2) Rheumatoid arthritis (non-specific infective arthritis, focal infective arthritis, atrophic arthritis)

(3) Ankylosing spondylitis (Marie Strumpell disease, von Bechterew's disease, spondylitis rhizomélique)

(4) (a) Osteoarthritis (chronic hypertrophic arthritis)
(b) Neuropathic joint disease

(5) Gout

(6) Traumatic arthritis

(7) Infective arthritis: e.g. gonococcal, tuberculous, pneumococcal

(8) Arthritis of allergy: e.g. serum sickness, systemic lupus erythematosus, erythema nodosum

A short article on a long subject suffers from sketchiness if comprehensive; from imbalance if selective. Only that part of rheumatism known as arthritis is considered here.

RHEUMATIC FEVER

The characteristic flitting arthritis with fever and tachycardia, usually preceded by a sore throat, seldom presents much difficulty in diagnosis. The response of the arthritis and fever to adequate doses of aspirin or sodium salicylate, and in some patients evidence of carditis—changes in the heart sounds and murmurs, pericardial friction or a prolonged P-R interval in the electrocardiogram—may be confirmatory. Rather similar joint involvement can occur in bacterial endocarditis; acute leukæmia and a number of other conditions accompanied by arthritis may cause confusion. On occasion acute febrile rheumatoid arthritis can mimic rheumatic fever but the effect of salicylate is usually less dramatic, although rarely there is a prompt response of the temperature and joint symptoms for a time, later to be followed by temperature escape and progressive joint involvement. When the diagnosis of rheumatic fever is questionable further observation and the results of a white cell count and blood cultures may be needed.

RHEUMATOID ARTHRITIS: MODES OF PRESENTATION

The textbook description of rheumatoid arthritis as a symmetrical, slowly progressive involvement beginning in small joints and occurring in young and middle-aged women is far too circumscribed for a disease which may have its onset from infancy to old age and be manifest in a variety of ways.

Vague ill health, joint and muscle pains, but objectively normal joints.—When a young man or woman presents with this history it is unwise to dismiss the symptoms as neurotic or hysterical. Especially if the blood sedimentation rate is elevated, is further observation likely to result in a diagnosis of rheumatoid arthritis. Preceding psychological or other stress should not be taken as evidence of a functional disorder, since such a history before the onset of rheumatoid arthritis is very common.

Monarticular onset.—Rheumatoid arthritis may be confined to a single joint for some time, most commonly the knee, but any synovial joint large or small may be affected. Biopsy is required to prove the diagnosis and is often mandatory to exclude tuberculosis. Orthopædic surgeons tend to regard monarticular arthritis as tuberculous, but it is clearly unjustifiable to perform arthrodesis whatever the clinical impression or radiological appearance until histological evidence has been obtained. While tuberculosis is becoming less common whereas rheumatoid arthritis is not, the chances of monarticular arthritis being due to the latter are increasing. In some patients whose symptoms are referred to a single joint careful examination reveals evidence of rheumatoid arthritis in other joints of which no complaint is made and unnecessary biopsy can thus be avoided.

Traumatic onset.—Persisting symptoms following a sprain, especially if soft-tissue swelling develops, is one mode of monarticular onset in which the patient's complaints may be mistakenly put down to the original injury.

Palindromic rheumatism.—This condition was originally described as a distinct rheumatic entity, but further experience suggests that it is a variant of rheumatoid arthritis since many of the patients eventually develop persistent joint involvement of rheumatoid type. The rather unusual use of the word 'palindromic' in the title means that the attacks are reversible, a palindrome being a word such as 'level' whose spelling is reversible.

The patient complains of multiple short-lived attacks of acute arthritis, usually limited to one joint at a time. Each attack lasts from a few hours to a few days, and a variable number, up to several hundred, may occur in the course of a year. Once the attack is over the joint returns to normal. Sometimes there is a para-articular as well as articular involvement. The joints affected may be exceedingly painful, red and swollen. The differential diagnosis is from malingering and hysteria, and gout. A history of exceedingly painful joint swellings lasting only a few hours with clinically normal joints when the patient is seen may arouse suspicions of either malingering or hysteria. The untreated acute gouty attack lasts up to two to three weeks and the attacks occur less frequently. The big toe joint is not favoured by palindromic rheumatism. Gout is rare in women and almost unknown before

the menopause. Occasionally serum uric-acid determinations may be needed but, in general, distinguishing between the two conditions is not difficult.

Periodic rheumatoid arthritis.—Apart from palindromic rheumatism, periodicity is a common feature of rheumatoid arthritis. When the remission cycle is long and complete and the attacks are short gout is often mistakenly diagnosed. Absence of the characteristic features of gout should in most instances point to the diagnosis.

Mild rheumatoid arthritis.—From time to time in general medical clinics one sees patients referred for other conditions who show unmistakable evidence of having had rheumatoid arthritis, often in the shape of ankylosed wrists. It is surprising how often such patients fail to remember any joint symptoms in the past. There is no doubt that very mild rheumatoid arthritis leading to no serious disability is common among the population.

Bagratuni's syndrome.—Bagratuni (1956) has drawn attention to what is probably an anarthritic variant of rheumatoid arthritis which may be puzzling. The patient, usually middle-aged or elderly, complains of severe pain in the muscles of the neck, shoulders and back and often of considerable disability with morning stiffness. A diagnosis of 'fibrositis' is likely to be made, but an elevated blood sedimentation rate (50 to 100 mm./hr.) is not a feature of ordinary fibrositis. Many of these patients make a good recovery but some go on to develop rheumatoid arthritis. A somewhat similar syndrome, to which the elderly are more prone than the young in my experience, is acute rheumatoid arthritis involving the hips and shoulders, and sometimes the knees, but sparing the peripheral joints.

Onset with painful feet.—It is not generally realized how often rheumatoid arthritis begins in the feet to which it may be confined for a long time. Many patients with 'foot strain', 'fallen arches', and 'plantar fasciitis' are in fact suffering from rheumatoid arthritis. Tenderness sufficient to make the patient wince when the metatarso-phalangeal joints are squeezed is extremely suggestive. Radiological changes are common, the earliest change being disappearance of the subchondral bounding line of one or more metatarsal heads, the forerunner of rheumatoid erosion.

Rheumatoid arthritis with œdema.—Pitting œdema of the hands and feet is a fairly common accompaniment of rheumatoid arthritis of acute onset. Sometimes the œdema may so dominate the clinical picture as to suggest a cardiac or renal origin, but absence of cardiac and renal disease and subsidence of the œdema with improvement of the arthritis show its cause.

CONDITIONS RESEMBLING RHEUMATOID ARTHRITIS

Psoriatic arthropathy.—Psoriasis may be accompanied by an arthritis broadly indistinguishable from rheumatoid arthritis, although recent research suggests distinction between them. Clinical differences between the two conditions are the tendency to early involvement of the terminal finger joints in psoriasis (occasionally arthritis may be limited to these joints, usually with psoriatic lesions of the nails), the greater tendency to osteolytic lesions in

psoriasis with the 'main-en-lorgnette' deformity, and of course the presence or absence of psoriasis of the skin. Sometimes the skin lesion may consist of a single patch which incomplete examination fails to reveal. A further difference between rheumatoid arthritis and psoriatic arthropathy is the tendency of the latter to involve the sacro-iliac joints and spine.

Reiter's disease.—The classical triad of conjunctivitis, urethritis and arthritis is easy to diagnose when all three components are present, but sometimes the other two may precede or occur after the arthritis. Keratodermia blenorrhagica of the soles of the feet when it occurs is diagnostic. This was once thought to be due to gonorrhœa but it now seems fairly certain that it is a feature of Reiter's disease, confusion having arisen from failure to appreciate that the latter and gonococcal urethritis may be present together. True gonococcal arthritis is very rare in ordinary practice, and I recall seeing only one proven case in the last ten years. So-called 'chronic gonococcal arthritis' probably never existed; the unfortunates so stigmatized seem to have been patients with rheumatoid arthritis and a positive gonococcal complement fixation test, an unreliable and misleading test, or those with continuing Reiter's disease. Although permanent joint damage is said not to complicate Reiter's disease, this is not so; bone erosions similar to those of rheumatoid arthritis develop in some patients. In a few patients Reiter's disease appears to result in a type of ankylosing spondylitis (Ford, 1953).

Pararheumatic arthropathies.—Joint involvement sometimes resembling rheumatic fever, but more commonly rheumatoid arthritis, may be a feature at some stage of any of the misnamed 'collagen' diseases, especially systemic lupus where it occurs in about 70 per cent. of patients. When arthritis is the presenting symptom, further observation, additional findings such as the presence of red cells and casts in the urine, or changes in the chest radiograph, may make the diagnosis clear. To add confusion to classification some patients with long-standing rheumatoid arthritis develop changes reminiscent of either systemic lupus or polyarteritis and the term 'malignant' rheumatoid arthritis has been used in this connexion.

Hypertrophic pulmonary osteoarthropathy.—This characteristically involves the wrists, knees, or ankles; finger clubbing is common but not invariable. The commonest associated condition nowadays is bronchial carcinoma and sometimes joint symptoms are the first complaint. The x-ray appearances of periosteal reaction extending from the diaphyses for a few inches up the shafts of the bones are characteristic. The condition often regresses when the associated pulmonary lesion has been dealt with.

Miscellaneous arthropathies.—Serum sickness as a cause of urticaria and painful joints is now uncommon, its place having been taken by penicillin reactions. Arthritis is an occasional complication of many conditions such as mumps, infective hepatitis, and glandular fever. One condition manifesting muscle and joint pains and sometimes true arthritis is brucellosis, to be kept in mind in country districts where pasteurization is by no means universal.

ANKYLOSING SPONDYLITIS

The poker back and characteristic fixation on walking and turning are seen in the advanced case. Earlier, complaint is made of low backache and stiffness, and sometimes of aching around the chest wall and in the shoulder girdle. The main complaint, however, may be of pain and swelling of one or both knees and, unless the back is examined, a mistaken diagnosis of rheumatoid arthritis or tuberculosis is entertained. Examination of a patient with early disease reveals limitation of spinal flexion and 'ironing out' of the lumbar curve. Similar symptoms are caused by many other low back troubles and the symptoms of a patient with ankylosing spondylitis are often attributed to 'low back strain', 'sacro-iliac strain'or 'vertebral displacement', depending upon the doctor's predilection for this or that unproven pathology before the correct diagnosis is made. The blood sedimentation rate is perhaps less helpful in suggesting the diagnosis than it is in rheumatoid arthritis.

Iritis is a common complication of ankylosing spondylitis; a history of this or eye changes indicative of past attacks is found in as many as 30 per cent. of the patients. There are families with a high incidence of ankylosing spondylitis and occasionally this may help diagnosis.

OSTEOARTHRITIS (OSTEOARTHROSIS)

The basic pathology being cartilage degeneration, with inflammation a secondary traumatic result, 'arthrosis' is preferable to 'arthritis' but osteoarthritis is in such general use that it is retained here. Since, after late adolescence, the cartilages of the weight-bearing joints begin to show signs of wear and tear, it is not surprising that osteoarthritis of some degree is inescapable with advancing age. The resultant symptoms depend upon its degree, its localization, and the pain threshold and general psychological make-up of the individual. Obesity is an accelerator. In general, osteoarthritis of weight-bearing joints is painful and sometimes disabling, whereas osteoarthritis affecting the hands is mainly unsightly. Trauma, either minor and recurrent, or major such as a previous fracture, is predisposing; nevertheless, unilateral osteoarthritis of the hip often occurs without obvious cause. The common types of osteoarthritis are as follows:—

Upper limb.—Heberden's nodes of the terminal joints should not be confused with any other condition. The swellings are bony but may be soft in their early stages. Osteoarthritis of the proximal interphalangeal joints ought not to be mistaken for rheumatoid arthritis, the spindling of which it may superficially resemble. Palpation confirms that the deformity is bony and not due to soft-tissue swelling. Apart from the carpo-metacarpal joint of the thumb and the acromio-clavicular joint, osteoarthritis does not commonly affect the other joints of the upper limb unless there has been antecedent trauma. Osteoarthritis of the shoulder is, for example, usually a mistaken diagnosis of sub-acromial bursitis.

Spine.—Degeneration of the intervertebral discs with consequent osteoarthritis of interfacetal joints leading to nerve-root symptoms from osteo-

phytes, especially in the cervical region, is common with advancing age. It is well to remember that some degenerative change throughout the spine is the rule in people over fifty, before accepting too readily radiological evidence of this as the cause of the patient's symptoms.

Lower limbs.—Moderate osteoarthritis affecting the knees is a source of discomfort rather than serious disability. Especially in women should the weight and psyche be considered in relation to degenerative changes whether clinical or radiological. As elsewhere the swelling is bony. Small effusions from internal trauma occur, but a large effusion usually, and soft-tissue swelling always, indicate another diagnosis. Severe osteoarthritis of the hip is a serious disability, the more so if bilateral. As pain in the early stages is often referred to the inner side of the knee, some limitation of hip rotation should be considered more significant than moderate degenerative change in the knee. In pain of spinal origin straight leg-raising is often painful and limited, whereas hip rotation is not; in hip disease the reverse is true.

GOUT

That gout is less common than it was a hundred years ago may be partly apparent rather than real, since rheumatoid arthritis was not separated as an entity until the beginning of the present century. Nowadays gout is often diagnosed when it does not exist, and is missed when it does. The following criteria have been found helpful. The acute gouty attack commonly occurs at night, involves the metatarsal joint of the big toe in 70 per cent. of cases, and rapidly achieves a summit of pain and hot shiny swelling. The untreated attack lasts from ten days to three weeks, after which the joint returns to normal. Desquamation towards the end of the attack is almost diagnostic. Constitutional symptoms are common, and the blood sedimentation rate rises to high levels during attacks. An acute arthritis coming on after surgical operation is nearly always gouty. Preceding trauma, compared with which the joint symptoms and signs are quite disproportionate, is common. Acute gout responds rapidly to phenylbutazone and colchicine, provided that the latter is given in proper dosage: i.e. 0.5 mg. hourly until gastro-intestinal upset develops. Radiology is unhelpful until the chronic tophaceous stage is reached. A raised serum uric-acid level is not so common as some suggest. Tophi are not often found in the early stages of the disease, the number of years they take to develop depending upon the frequency of attacks and hence the rapidity of progress to the chronic stage.

Gout runs in families but a family history seems to be obtainable from only a proportion of patients, the proportion depending upon the social class and the stability of the population: i.e. 'top people' tend to have accurate information about family history and family diseases. It cannot be too strongly emphasized that gout is rare in women and almost unknown before the menopause. The differential diagnosis is from acute infective arthritis, palindromic and episodic rheumatoid arthritis, cellulitis, and traumatic episodes in hallux rigidus and osteoarthritis of the great toe.

Chronic tophaceous gout.—A chronic deforming arthritis with tophi in the hands, olecranon bursæ, ears, and nasal cartilages should not give diagnostic difficulty. The serum uric-acid level is almost always raised. The radiological appearances, however, are by no means always distinctive since similar 'punched-out' areas are seen in rheumatoid arthritis.

LABORATORY TESTS IN RHEUMATIC DISEASES

The blood sedimentation rate.—This is the simplest and most useful single test. The Westergren is the easiest and most satisfactory method. A raised B.S.R. is found in most of the inflammatory arthritides, but 10 to 20 per cent. of patients with clinically active rheumatoid arthritis have a normal B.S.R. (Fearnley, 1957).

The sheep-cell agglutination test.—About 60 per cent. of patients with rheumatoid arthritis have a factor in their serum which agglutinates sensitized sheep red cells at high titre. The result is expressed as the titre to which sensitized cells are agglutinated divided by the titre to which unsensitized sheep cells are agglutinated. A result of 1 : 16 or greater is positive. Positive results are also obtained with some of the collagen diseases.

The L.E. cell phenomenon.—The demonstration of L.E. cells in the blood is more or less diagnostic of systemic lupus erythematosus. The test is of value in elucidating patients with arthritis and additional unusual features.

Serum uric-acid level.—It is preferable to measure uric-acid levels in serum rather than blood. Normal values are 3 to 6 mg. per cent. Provided kidney function is normal and the patient is not suffering from leukæmia, levels greater than 6 mg. per cent. are indicative of gout or the gouty diathesis. The serum uric-acid level fluctuates, however, and it is advisable to make several determinations before accepting that the level is within normal limits. It should be remembered that aspirin, sodium salicylate, and phenylbutazone cause a uric-acid diuresis with lowering of the serum levels.

CONCLUSION

A careful history and physical examination, supplemented by a B.S.R., will, in the great majority of patients, enable a correct diagnosis to be made. Sometimes radiology and other laboratory tests will be needed but in diagnostic value the history and examination can be said to rate 80 points out of 100, leaving 20 points to special investigation. On the other hand, cursory history-taking and examination limited to the site of pain bring a proportionate award of meagre diagnostic success. Although few of the arthritides are susceptible to cure, accurate diagnosis is essential to differentiate between the trivial, the self-limited, and the serious, and is the bedrock of the management of the patient.

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SOCIAL ASPECTS OF RHEUMATOID ARTHRITIS AS SEEN BY A CLASS OF MEDICAL STUDENTS

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The method of instruction in social medicine whereby fifth-year medical students of the University of St. Andrews visit in their homes patients suffering from a particular disease has already been described (Mair, 1957). The object of this article is to review the results of such visits during the academic year 1955-56, when rheumatoid arthritis was chosen as the disease for special study.

ORGANIZATION

A total of 67 patients suffering from rheumatoid arthritis were visited in their homes by a similar number of medical students.

The names of patients residing in the city were obtained from the records of two Dundee teaching hospitals and of an orthopædic and physiotherapy clinic. In addition, four general practitioners were asked to submit names of patients known to them. It was found that these lists overlapped to some extent.

Of the patients who were over 65 years of age, only five were included in the survey, as it was felt that the social problems of older age-groups might be more stereotyped than those of younger patients and would exclude employment problems. These five patients, and 62 of the younger ones, were then allocated to students.

The general practitioner concerned was contacted before any visit was paid and it was in many cases found that he voluntarily made a preliminary call, in order to pave the way for the student's arrival. The number of visits paid to each patient was left entirely to the student concerned. Some accomplished their task in one prolonged visit, but the majority paid several—usually a brief introductory one, followed by one or more longer visits. The time taken to gain the confidence of patients and their families varied, but this objective seemed almost always to have been attained in the end.

The success or failure of these visits must lie in the impression of rheumatoid arthritis and its social problems obtained by the students. The subsequent discussion groups, involving students, general practitioner, almoner, health visitor, and university teacher, helped to clarify this and to translate it from an individual impression to a more balanced group appreciation of the factors involved. There are obvious shortcomings in attempting to sum up the reports on 67 different patients brought back by 67 different students. As was often seen at the case conferences, students varied in their approach to the different aspects of the investigation. Thus some stressed one particu-

lar feature whereas others minimized it. For example, some students were more interested in the effects of rheumatoid arthritis on employment, others paid more attention to its consequences within the family, whilst a few appeared to be more concerned with the purely clinical aspects of the disease. The composite picture which emerged must therefore be judged with that

Age	Males	Females
60+	—	1
55+	1	1
50+	1	10
45+	3	2
40+	4	14
35+	2	5
30+	3	6
25+	2	4
20+	1	5
15+	—	1
10+	1	—
−10	—	—
Totals	18	49

TABLE I.—Age at onset of rheumatoid arthritis.

in mind, but on the whole these variations in emphasis tended finally to cancel one another out, leaving a reasonably balanced picture. It is, after all, no more likely to be false than is a retrospective review of some disease written up from hospital records, when bias is inevitably introduced by the multiplicity of housemen who wrote the original case histories.

MEDICAL ASPECTS

Of the 67 patients, 49 were female and 18 male, giving a female/male ratio of 2.7 : 1. This is the same as that described by Duthie *et al.* (1955) and is comparable with other published reports. Their ages ranged from 21 to 72 with a mean of 49.6 years: 43 per cent. were in the 45-54 age-group. The age at onset (table I) revealed that over half the females suffered their first symptoms between the ages of 40 and 55 years and that the males, although fewer in number, showed a similar trend. The mean age at onset was 38 years in males and 40 years in females. This is slightly lower than the figures of 42 and 41 respectively quoted in the report of the Empire Rheumatism Council (1950) and is no doubt accounted for by the exclusion, already mentioned, of the more elderly patients.

As commonly occurs, patients offered many and varied explanations for the onset of their arthritis. Dampness in some form was blamed in 27 instances, this having occurred at work in eleven cases, from a soaking in eight, in the home in two, and elsewhere in six. Nine patients blamed the onset of the disease on injury to a joint, nine mentioned other diseases as possible etiological factors, eight offered other vague explanations, and fourteen stated that they could think of no possible cause. The joints most commonly affected in the first instance were those of the hands and wrists,

followed by the feet and ankles and then the knees. In all but two cases the disease had subsequently advanced to involve other joints.

Treatment covered the usual medicinal range from aspirin through various analgesics to cortisone and, as is typical in rheumatoid arthritis, the variable opinions expressed on the value of different preparations presented no clear picture. Of the patients, 25 had received treatment only in hospital, 21 only as outpatients and 20 had received both, whilst one had been attended exclusively by his general practitioner. The outpatient attendances had been almost entirely for the purpose of physiotherapy, and some patients had continued with exercises or wax baths at home.

HOUSING

Three-quarters of the patients lived in tenements or flats. Of these, only seven were situated on the ground floor, 22 being on the first, 15 on the second, and six on the third floor. As none of the buildings concerned was equipped with a lift, the inconvenience to the more incapacitated patients is obvious. Duthie (1951) mentions the futility of returning such patients to the top flat of tenement houses. The number of rooms per house (including the kitchen if used as a living room) was one in four cases, two in eighteen, three in twenty-five, and four or more in the remaining twenty. The houses were overcrowded in terms of the Housing (Scotland) Acts in only four cases, but if the more satisfactory standard of one person per room was applied, the figure rose to 16, or about 25 per cent. of the houses concerned. Perhaps a better idea of the living conditions is obtained by a consideration of the sleeping accommodation. In the 63 cases in which clear information was available, it was found that only 37 patients slept in a proper bedroom, the other 26 sleeping in the living room or kitchen. The room in which the patient slept was shared by three or more persons in seven instances.

The communal water closet, which is such an objectionable feature of Scottish tenement life, was used by 19 of the 67 patients (28 per cent.). As this is usually situated on the stairs between two floors and is often cold, it constitutes a particular burden for patients with rheumatoid arthritis. A proper supply of hot water was commonly lacking. No less than 24 patients (36 per cent.) lived in houses where all water had to be heated in kettles and the constant transporting of these constituted an especial burden and danger to housewives afflicted with rheumatoid arthritis. The soothing and beneficial properties of a hot bath could not, of course, be enjoyed at home by these patients; indeed only 32 patients (48 per cent.) had fixed baths in their homes. A further 5 (7 per cent.) had movable 'tin' baths and 9 (13 per cent.) tried to make up the deficit by inconvenient visits to public bath-houses.

Information on the arrangements for clothes washing was obtained in every case.

Over half the families (35) performed this task in the household sink and 12 used communal wash-houses. Three female patients and their families were obliged, by rheumatoid arthritis, to send their washing to the laundry, with attendant expense; three had it done for them by neighbours; and the surprisingly high number of 14

(over 20 per cent.) used washing machines. This last method was again usually adopted as a means of overcoming the difficulties in washing caused by rheumatoid arthritis in housewives. Four families had inadequate outdoor drying facilities and a further six were obliged to do all their drying indoors, thus causing an unpleasantly damp atmosphere in the kitchen.

Rents, in the 60 cases in which details were volunteered, varied from less than 5*s*. a week (two patients) to over 30*s*. a week (two patients), with 80 per cent. paying less than £1 a week.

Whilst these various details may give an outside observer's idea of the adequacy of the housing of patients, the patients' opinions of their conditions are at least equally important. Of the 66 patients who expressed their opinions, 37 were satisfied with their houses and 29 were dissatisfied, in several cases for multiple reasons. Some wanted a house with a bathroom, believing that hot baths would help their condition; some wanted a house on the ground floor; some wanted a house with an indoor W.C.; and some wanted a house nearer their relatives or places of employment. Incidentally, despite these complaints and defects, in only four cases (6 per cent.) did students consider the houses to be lacking in cleanliness and in only 2 (3 per cent.) did they make similar remarks about the patients.

OCCUPATION

Nine of the 18 males in the survey and 13 of the 49 females were gainfully employed. Allowing for one male and 18 females who were not normally in employment, either because of age or marital state, there remained eight

Category	Occupied	Unemployed
Clerical	2	3
Manual		
Skilled	10	7
Semi-skilled	6	8
Unskilled	3	7
Apprentice	1	1
Totals	22	26

TABLE II.—Occupations of 48 patients with rheumatoid arthritis.

males (47 per cent.) and 18 females (58 per cent.) who were unemployed (table II). Of those in employment, one male and one female were engaged in clerical work; five males and five females were in skilled, three males and three females in semi-skilled and three females in unskilled manual work. One female was an apprentice. As regards physical effort, none of these jobs was classified as heavy, eight jobs for either sex being medium and one male and five female jobs involving only light work.

On investigating the occupational history of the 22 patients who were gainfully employed, it was found that nine (41 per cent.) of them (five men and four women) had been obliged to change their employment as a direct result of the disease, in all cases seeking either lighter work or work with more suitable hours or working conditions.

For example, a tram driver successfully started a one-man taxi business to obtain a drier and warmer job; a sewing-maid was obliged to become a telephonist because of the advance of disease in her hands; a worker in a fruit canning factory changed to a dry-cleaning establishment; and a manageress of a bakery shop changed to the shorter hours of managing a launderette. A joiner was obliged to seek joinery involving only indoor work, and a railway signalman had to be transferred to a box where the work was less heavy.

These patients, often in middle-age, had to readjust themselves to new employment after the onset of the disease, and this usually called for considerable determination.

All but two of these patients were working a 40-hour week or more but only three found themselves able to participate in overtime work. It was interesting to note that, whilst most of these employed patients had at some time received physiotherapy, none had ever been subjected to a comprehensive scheme of rehabilitation designed specifically to render them fit for employment and only four were registered under the Disabled Persons (Employment) Act. All but one had found their current jobs by their own efforts and all but three were reasonably satisfied with the results.

Of the 26 patients who were unemployed, 23 were in that state because of rheumatoid arthritis and, compared with the 22 in employment, a relatively higher proportion of the unemployed belonged to the category of unskilled manual workers. In other words, as work becomes less skilled and thus usually heavier, so the employment prospects of patients suffering from rheumatoid arthritis diminish. None of the patients in employment was classified as having a heavy job. Only 12 of the 26 were registered under the Disabled Persons (Employment) Act and none had undergone any comprehensive form of rehabilitation. This was singularly unfortunate for, as many authorities (e.g. Ragan, 1949) stress, rehabilitation is an essential step in the successful treatment of patients suffering from rheumatoid arthritis.

The plight of some of the unemployed patients, especially in the younger age-groups, was sad.

James C., now aged 21, was 13 when the first symptoms of rheumatoid arthritis appeared. At first only the joints of the lower limbs, especially the ankles, were affected, but the arms, neck and hands became involved within a year. On leaving school at 15 he obtained employment as an apprentice motor mechanic but had to give up work within six months because of difficulty in bending and weakness of the hands. He has been completely unemployed for the past six years, passing the time with the help of radio, television or books, and occasionally doing a little woodwork when his hands are not too stiff. His prospects of employment are poor, as one of his legs is so badly affected that he cannot mount the platform of a bus. The same leg makes prolonged sitting in a straight-backed chair uncomfortable, and the strength of his hands is so poor that he could tackle only very light work.

ECONOMIC FACTORS

It was felt that it might not be good policy for students to delve too deeply into the economic situation of the households visited, as patients are often much more reticent about their incomes than about their health. Questions were therefore directed towards establishing the number of wage packets coming into the household rather than towards their contents; and more

towards learning the nature of any economic hardship rather than its precise monetary size. In 42 cases (63 per cent.) there seemed to be few economic difficulties because one or more other members of the family were out at work. The economic hardships which were complained of lay most commonly in unemployment, the next most commonly mentioned being the necessity for extra clothing. A few spoke of the need for special food or extra entertainment in the form of television for the patient. Some mentioned more than one of these factors.

The students considered the general economic state of the families to be reasonable or better in 45 cases, fairly good in 16 and poor in six cases.

EFFECTS OF ILLNESS ON FAMILY

These were varied. Whilst the students considered that in only seven cases was much extra work involved in the household because of the patient, in five further instances it was found that other members of the family were obliged to go out to work to supplement the income. In 25 families holidays had to be restricted, either because the patients' rheumatoid arthritis made them physically difficult or because of economic difficulties consequent upon the disease. Thus, 25 patients who stood in greater need of holidays than healthy people were unable to obtain them. The presence of a disabled person in the family tends to be a strain on the other members, yet in only six cases did students report any obvious friction during their visits. Most families seemed to accept the position and only four appeared to react to it by an exaggerated fear of the disease.

Again, the problem of hobbies and leisure activities can be of great importance both to patients and families in a disease such as rheumatoid arthritis. Only 8 patients appeared to have no interests whatsoever. Most of the remainder had one or more activities, the order of frequency of mention being passive indoor hobbies (e.g., wireless, television, reading) 36; creative indoor activities (e.g., knitting, sewing, artistic work, joinery) 32; physical activities (e.g., sports, games, dancing) 13; others 23. It was surprising to find that 55 of the 67 patients belonged to no outside organization, club or society.

DISCUSSION

In so far as the visits were intended to show the students the social rather than the clinical side of the disease, the brevity of the clinical reports is not of great moment. Full opportunity of learning this side of the disease occurs in the class of systemic medicine, in hospital wards and in outpatient departments.

On factual matters, the social reports were likely to be reliable. Thus, details of overcrowding, sleeping arrangements, washing facilities, occupation, and leisure activities could be expected to be recorded precisely. It was on matters of opinion and subjects calling for practical experience of social and economic conditions that difficulties occurred. These difficulties became apparent in the discussion groups. There was a lack of unanimity on such

matters as what made an adequate income for a given family, what constituted good management of the household budget, and what constituted an adequate reason for giving up or changing jobs. From a research point of view, these visits were therefore of very limited value. The students concerned had not completed their training either in clinical medicine or in social medicine and lacked practical experience of what they had learnt in both these subjects. The multiplicity of observers reporting individually on so wide a variety of patients likewise reduced the potential research value of the results.

There are, in other words, distinct limitations to such an investigation by multiple observers with limited experience of this type of interviewing. Furthermore, if the results were to be used for research purposes it would be essential to select patients by some more random method and this might well lower the educational value of the work, as it is no doubt true to say that it is only a minority of patients suffering from any particular disease who present pressing social problems. Also, except in the cases of comparatively uncommon diseases, it would be difficult to scale an adequate random sample down to the number of students taking part in the survey.

What the scheme did accomplish far outweighed these limitations. The discussion groups amply confirmed that most students had been acute in their observations during visits and had, in general, managed to acquire a reasonable understanding of the social conditions of patients. The presence of the family doctors enabled the point of view of medicine as it is most widely practised—as distinct from that rather cultivated rose, hospital medicine—to be put before the students for the first time in their training. It was encouraging to find that differences of opinion—sometimes quite sharp ones—arose between members of discussion groups. The thrashing out of these differences often led into fields at first sight remote from medicine, yet, as gradually became clear, relevant to the complete picture of the patient in his environment. It soon became apparent that all taking part, whether students or staff, were finding something of value in this method of teaching social medicine.

SUMMARY

A small-scale survey of the social aspects of rheumatoid arthritis is described. This work was carried out by medical students as part of their training in public health and social medicine.

I am grateful to those doctors, almoners and health visitors who were mentioned in Professor Mair's article (Mair, 1957) on this subject, and also to Miss M. McRostie, Miss A. Brinkler and Miss M. Nicoll for their help in analysing and preparing the results of the survey for presentation.

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THE SELECTION OF DEPRESSED PATIENTS FOR ELECTROCONVULSIVE THERAPY

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' . . . tell us, pray, what devil This melancholy is, that can transform Men '.—'The Lover's Melancholy', John Ford (1629)

DEPRESSION is a common feeling, and depressive states are those most commonly met with in psychiatric work. Watts (1956, 1957) has stressed the importance of recognizing these conditions in general practice, and his careful survey reveals that on the average a list of 2000 patients will yield a minimum of ten sufferers from endogenous depression in each year even if many of these go undiagnosed for long periods. Endogenous depression is not only common, it afflicts mostly those who are the salt of the earth, the reliable, capable and conscientious people of this world, not only after their work is achieved, but just as often in their prime.

It is a humbling example of biological complexity that 'reactive' and 'endogenous' depression, contrasted for so long in textbooks, have not been proved as separate entities. Of all the varieties described in textbooks, whether 'reactive', 'recurrent', 'agitated', 'involutional', or 'atypical', the important thing is that those with the features of endogenous depression, to be described, are most likely to be helped by electroconvulsive therapy (E.C.T.). In this article, emphasis is not placed on the differentiation between such categories but on picking out the patient suitable for E.C.T. on the basis of a single interview.

It is unnecessary to know anything of formal psychopathology to diagnose endogenous depression, nor is it needful to take a full psychiatric history. The most important aspect of the diagnosis is to bear the possibility of this common reaction in mind. The symptomatology is, as a matter of fact, easy to remember, and most of the questions to be asked are not such as to lead a patient to suspect that a psychological cause of his or her illness is being sought. Whilst there is often little doubt about the diagnosis before physical examination, this is undertaken not only to exclude an organic cause but to reassure the patient that his symptoms are not the result of the disease he has probably diagnosed himself.

IMPORTANCE OF EARLY DIAGNOSIS

One need only refer to the case-histories of patients who suffered from melancholia (severe endogenous depression) fifty years ago to appreciate the natural history of this condition: an average of eighteen months' abject

misery, utter hopelessness and despair, with physical debilitation resulting from refusal of food, punctuated by suicidal attempts which not infrequently were attended by final success. Nowadays, even in a severe case, six weeks off work is the most a patient usually needs, and this includes therapy as well as a reasonable period of observation for the physician to be fairly certain that a slip back is unlikely. A still more important advance is that, since endogenous depression develops slowly in most instances, the severe and advanced picture can often be completely avoided by early diagnosis and treatment as an outpatient, the patient remaining at work on the four weekdays when treatment is not given. It is a happy characteristic of depressive illness, of which sufferers should be constantly reminded, that once recovery has occurred there is no impairment of mental integrity.

Whilst it is true that almost all endogenous depressions are self-limiting, the extent to which severe symptoms will appear in an individual can only be reckoned in retrospect. The process is autonomous and relatively unaffected by the environment. As time goes on, the risk of suicide increases unless the patient becomes so retarded or indecisive as to be unable to effect the deed. The sufferer who has finally decided to ask medical help, half believing that he is beyond human aid and convinced that he is eternally damned, is likely to seek a quicker way out if this help is not forthcoming. The cases reported daily in the press as 'suicide while the balance of his mind was disturbed' are often the result of undetected endogenous depression.

ENDOGENOUS DEPRESSION

Endogenous depression is rare before 20; it is seen especially in middle and later life. Although the onset is generally insidious, a precipitating factor can often be found. The symptoms may begin in the presence of organic disease such as hypertension, cardiac failure, myxœdema or pernicious anæmia; but it is perhaps commoner during convalescence from debilitating illnesses, especially virus infections, 'flu being a notorious offender. In women, the puerperium and menopause are particularly vulnerable times. Certain drugs, such as the antibiotics and rauwolfia, may induce endogenous depression, the mental symptoms often not appearing until the medicine has been exhibited for some weeks, or even after it has been stopped. In the psychological sphere, bereavement, disappointment, retirement, promotion, or the sudden cessation of prolonged strain may trigger off the essentially endogenous process.

Although individual histories vary greatly in detail, the over-all pattern in endogenous depression is surprisingly similar in the vast majority. The symptoms and signs themselves may be regarded as evidence of a damping-down process affecting the whole of psychic and bodily activity. The lowest level of an untreated patient with depression who has not committed suicide is complete inertia, the patient being in stupor. Present knowledge of the physiology of this process is far from complete, but there is no doubt that many of the depressed patient's symptoms are based on facts which can be

objectively verified: for example, a slowed pulse rate, sluggish vasomotor responses, lessened salivary secretion, diminished tone and peristalsis in the alimentary tract, dry skin, loss of weight and diminished or absent menstruation. Recent evidence indeed suggests that a biochemical mediator is in some way responsible for the widespread changes occurring in endogenous depression, the mental changes being secondary. The remarkable response to E.C.T. could be more easily explained on this basis, and it helps to explain why the patient cannot 'pull himself together', despite advice from his relatives, friends, employer or, alas, doctor.

THE THREE CARDINAL SYMPTOMS

To judge by the textbooks, the symptoms of endogenous depression seem so diverse, the concept of the illness so vague, the varieties so numerous, and atypical cases so common, that the diagnosis often appears a remote possibility. The situation, however, is not as gloomy as it first appears. As in many illnesses, there are a few cardinal symptoms on which the diagnosis ultimately rests and one should not wait for the full-blown picture to develop before taking action. These cardinal symptoms occur early—they indicate not only that the depressive state is a pathological one, but also that, fortunately, the chances of recovery by means of electroplexy are high.

(1) *Sleep disturbance.*—The following pattern is pathognomonic. There is no difficulty in falling asleep at the usual hour at night, but the patient wakes in the early hours of the morning between midnight and 5 a.m.; he is occasionally awoken by nightmares or tragic dreams. There is difficulty in getting to sleep again, due to morbid thoughts, feelings of hopelessness, or maybe of past guilt or various hypochondriacal sensations. If sleep is regained at all, it is broken long before dawn, the patient snatching short periods of slumber only to wake once more after an hour or so. Fitful sleep is common and some patients lie in a twilight state, half-asleep yet half-awake, giving an outward appearance of repose but later feeling no benefit. As the process develops, the patient follows his usual habit of retiring but spends the hours of darkness restless and desperate. Sedatives in moderate doses are ineffective in preventing this early waking, and any patient whose presenting complaint of insomnia follows this course should be closely examined for further evidence of endogenous depression. Through knowledge of this pattern of sleep disturbance alone, the differential diagnosis from anxiety state, neurasthenia, hysteria or obsessional state may be made in practically all cases.

(2) *Diurnal mood swing.*—The patient's sufferings, whatever their content, nature and severity, are worse in the morning shortly after waking. It is often reported that immediately after waking there is a short interval during which the horizon is clear, only to be followed by a descending cloud of depression when all other symptoms return. As the day wears on, the patient's troubles become less obtrusive. There may be a relapse after a daytime nap or after lunch but the evenings are always the best time of day. The swing of emotion

may be extreme with feelings of suicide in the early hours and normal capacity for enjoying life in the evening. In late cases, the evening lift does not take place and the whole day is wrapped in gloom. When bodily complaints are the most obvious feature, these, too, become less as the day passes; this applies also to retardation, powers of concentration, energy, drive and interest.

(3) *Retardation.*—This is a slowing-up process of thought and movement to be noticed in many cases. The patient pauses inordinately long before replying to questions but then answers them slowly, accurately and honestly. Speech is slow and laborious, as are bodily movements, and there is poverty of mental associations. Emotional expression in the face may be entirely absent. Even if a smile can be raised, it is a slow-motion caricature, and amusement shown by the eyes precedes it.

These three symptoms together indicate endogenous depression, whatever the variety of somatic complaints accompanying them. Of the three, the first is the most likely to be presented by the patient unprompted. If but one of the three is found, it is still a strong pointer to the same diagnosis.

OTHER SYMPTOMS

Bodily symptoms.—Aches, pains and sensations of all kinds, referred to one or many parts of the body, are common presenting symptoms in the early case. Many of these manifestations remain unexplained in terms of altered body function but the three most important and constant 'hypochondriacal' symptoms—loss of appetite, loss of weight and constipation—have some physiological basis. Loss of appetite appears long before delusions have developed to account for the refusal of food and is dependent upon poor gastric tone, diminished secretion and motility, as well as on loss of interest in eating. Loss of weight is often marked and may be out of proportion to the diminished food intake, poor absorption playing a major role. Constipation is consequent on sluggish intestinal activity and diminished food and fluid ingestion. Loss of libido, exhaustion and disordered menstruation can be deceptive presenting symptoms.

Later, hypochondriacal delusions form on the basis of earlier somatic sensations. These are often bizarre. A persistent aching pain in the chest convinces the patient that he has galloping consumption or that his chest is being eaten up by worms; the unrelieved constipation can only be due to bowels hopelessly blocked by cancer and no further food should be taken to aggravate the stoppage. No amount of good sense, sympathy, logic or symbolic interpretation can penetrate and dispel the severely depressed patient's self-occupation with such topics.

Symptoms associated with retardation and self-preoccupation.—Frequent complaints in this sphere are lack of energy, lack of drive, lack of initiative, inability to cope, inability to work, to listen to the radio or to watch television, despite previous enjoyment of such pursuits. Having to force himself to do things, and postponing things from day to day, are fairly common symptoms

appearing in previously active and conscientious personalities. Lack of concentration, indecisiveness and inability to be sociable are further crippling symptoms. The patient often notices a lack of the usual emotions towards his nearest relatives. In the face of such inadequacies, he often fears impending insanity. Such developments occurring in middle and later life are most likely to be due to endogenous depression.

Feelings of guilt, paranoid ideas and suicide.—The endogenously depressed patient blames *himself* for his troubles, placing particular emphasis on his inadequacy. Other people may be implicated by relatives but never by the patient. Feelings of guilt and self-reproach gradually develop into delusions centred round a nucleus of past truth. Past and forgotten peccadilloes are resurrected and magnified to account for the feeling of guilt. A strong moral flavour attaches to these delusions, hence venereal disease is an ideal topic since it provides the patient with a reason for his somatic sensations as well. Other complaints often heard are that the patient feels 'a fraud' or is a burden to his wife and family—the latter usually means that a planned suicide is not far distant.

Particularly in elderly subjects the delusions show a paranoid trend. The patient is persecuted, shadowed, searched for; he wakes regularly in the early hours to hear planes searching for him, and during the day the police eye him knowingly. The underlying theme, however, is guilt and he confesses that he is to blame and deserves punishment. He may go to the police with the delusion that he has been guilty of murder, or allowed his family to starve by neglecting his work. To his chagrin, he is not believed. He may commit suicide to avoid disgrace, or merely not to be 'in the way' any longer. Delusions of poverty, of having no clothes to wear, are usually late in appearance. Feelings of unreality are often encountered at all stages of the illness.

ADDITIONAL POINTERS TO THE DIAGNOSIS

Because the practitioner is most commonly faced with an unaccompanied patient in a busy surgery, attention has so far been directed to the symptoms and signs given by the individual sufferer. Further helpful information may be obtained from the nearest relative, especially towards establishing perspective as to the patient's present state in relation to his previous personality. This is important because depression, whenever it descends, tends to evoke symptoms coloured by the patient's normal disposition. A rigid, obsessive man will show obsessional symptoms when depressed; a histrionic woman will show overt hysterical signs and be more importunate than ever. Those with a tendency to anxiety will show anxiety manifestations in abundance. Superficially, the clinical picture in such patients is one of neurosis, but the appearance of neurotic symptoms for the first time in middle or later life is almost always due to underlying endogenous depression. Whereas the tendency to develop a pure neurosis decreases with increasing age, the risk of developing endogenous depression increases.

Episodes of similar symptoms in the past, lifting spontaneously or with E.C.T., often help to confirm the true nature of the present attack as a depressive one. These, too, will have been coloured by the prevailing personality and the history may therefore be of recurrent attacks not only of depression, but also of hysteria, obsessional state or alcoholism which tended to mask it. The simultaneous presence of the cardinal symptoms mentioned above provides the clue.

Advancing years are no bar to the illness and the increasing longevity of the populace therefore augments the depression-prone population. Depression supervening at this time may produce a picture of delirium or dementia. A careful search will usually reveal sleep disturbance and diurnal mood variation, and delusions of poverty with consequent agitation are more common. These patients do equally well with electroplexy, and the excellent prognosis of the depressive element is qualified only by the degree of organic cerebral disease existing before the onset of the affective illness.

E.C.T. OR NOT?

Every patient with endogenous depression is likely to benefit more from the administration of E.C.T. than from any other treatment. It is therefore important that no patient in need of this should be denied it. In practice there is no physical contraindication, since almost invariably the psychiatric illness dominates the case. The stigma once attached to a patient who consulted a psychiatrist is now a thing of the past. If there are any doubts concerning the efficacy of E.C.T., they should be vigorously neutralized; far from permanently disturbing mental processes or interfering in any way with a person's natural talents, all the evidence suggests that in properly chosen cases, including all those with endogenous depression, the capacity to enjoy life in the broadest sense is restored along with the feeling of being oneself again.

It is reassuring to the patient who is likely to need this form of therapy to know from the onset that it is usually given twice a week, that the average number required is four to six, that complications are exceedingly rare, and that mild memory disturbance affecting recall is transient and lasts, in most cases, only a matter of weeks after the cessation of treatment. The essential process lasts only half a minute and in the majority of clinics nowadays, thiopentone anæsthesia and a relaxant are used to minimize anxiety and the convulsion. The 'dose' of electricity is strictly limited by the machine at a safe level. Improvement is evident objectively after two or three treatments, but it is only after the fourth that most subjects will admit a change for the better. The over-all recovery rate with E.C.T. in all types of depression is 70 per cent. (Thomas, 1954) and, although it is as low as 35 per cent. in 'reactive' cases, it is well worth trying in these too; the temporary improvement helps the patient to endure the otherwise prolonged period of intense suffering.

IS THE PATIENT SUICIDAL?

This question must always be answered before any depressed patient leaves

the surgery. Suicidal thoughts are perhaps the most potent indication of the need for inpatient care and, if occurring in endogenous depression, the need for electroplexy is urgent. The exact mode of inquiry will be individual, but a series of questions of increasing significance, each one justifying the next, should be put to the patient after he has described his feelings of hopelessness, gloom or despondency. The following queries may be put: 'How do you feel in your spirits?'; 'How do you feel in yourself or in your mood?'; 'How unhappy do you feel?'; 'Do you feel you can carry on?'; 'Do you think that life is not worth living?'; 'Have you ever thought of a way out?'; 'What did you think of doing?'; 'Have you ever tried to end things?'. It is usually unnecessary to continue the series to the end, which is fortunate as it avoids putting ideas into the patient's mind, and there is the additional advantage that each successive question gives a more concrete idea of the likelihood of suicide. If a reply is obtained (with unaverted eyes) 'I would never think of suicide because of my religious principles' or 'because of my family' the risk is a small one. A patient with formulated ideas or plans of suicide, however, or one who has recently made an attempt on his life should be in hospital.

Almost all patients with endogenous depression are scrupulously honest in this matter and will answer questions truthfully if asked. Only by asking can one avoid missing the potential suicide in the form of the 'smiling depression'. If the doctor has doubt after this, he should obtain a promise from his patient not to attempt suicide and to contact a responsible person should he feel desperate; the patient's reply will throw future probabilities into relief. These statements apply equally well to reactive depressions since a severe enough emotional blow in an unstable person may well create suicidal intent. A histrionic statement should never be disregarded. Demonstrative attempts do sometimes succeed by mistake and even hysterical personalities can develop severe depression. Particular care should be taken with the uncommunicative or secretive patient, and also with those showing obsessional features. Moreover, there is a greater risk in those who are agitated and active than in those who are severely retarded.

CONCLUSION

In conclusion, if every case showing the cardinal features were to be referred to psychiatric 'outpatients' early, not only would the overcrowding in mental hospitals be greatly eased, but also the doctor who identified only one case among his 'functional', 'neurotic', or 'hysterical' patients would find great personal satisfaction. The successful treatment of a severe endogenous depression by E.C.T. is often quick, simple and gratifying to patient and doctor.

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THE REDUCTION OF DIFFICULT DISLOCATIONS OF THE JAW

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Reduction of a recent unilateral or bilateral dislocation of the jaw is not generally difficult to accomplish by the traditional manipulations. The operator presses the angles of the jaw downwards with the protected thumbs on the molars, and raises the chin simultaneously with the fingers outside the mouth. An anæsthetic may be necessary, and the manipulation will be found easier to do if the patient lies on the floor. When this method does not succeed, it is possible to obtain greater leverage by the insertion of a cork between the molar teeth on each side; this leaves the hand freer to exert upward pressure on the chin. Textbooks do not explain how to remove the cork from the clenched teeth after reduction, without reproducing the dislocation—an occurrence which I have seen on two occasions. Whichever method is used, the patient wears a bandage to support the jaw for ten days after reduction.

TWO METHODS

It sometimes happens in muscular patients with powerful jaws that neither of the above methods achieves reduction. This has been the case among the Congolese of Central Africa. In such cases, a relaxant, if available, would undoubtedly facilitate the manœuvre, but the services of professional anæsthetists are not easily available in Africa. The following method has proved useful in resistant dislocations:—

One or two anæsthetic gags are used, according to whether the dislocation is unilateral or bilateral. The patient lies on the floor, and the assistant inserts the gags between the molars, while the operator sits astride the patient.

The assistant is ready to force the jaws open by closing the gags at the moment when the operator exerts upward pressure with one or both closed fists under the chin. The gags can be closed by hand pressure, or by slowly tightening the screw stop provided (fig. 1).

As soon as the characteristic click of reduction occurs, the assistant releases the gag and withdraws it.

In a recent case of bilateral dislocation of the jaw in an African of muscular build, it was possible to reduce one side by this manœuvre after failure of traditional methods, but the other side resisted all attempts at manipulation. Reduction was finally achieved as follows:—

The patient was anæsthetized with intravenous thiopentone, and a

1-inch (2.5 cm.) horizontal incision (with local anæsthesia) was made immediately below the zygomatic process over the palpable articular process of the mandible. A small bone lever was insinuated under the zygomatic process and in front of the mandibular condyle. Using the

FIG. 1.—Method for reducing a difficult dislocation of the jaw, using two anæsthetic gags.

zygomatic process as a fulcrum, it proved easy to reduce the dislocation, with an assistant performing the usual manœuvre within the mouth, but not without his help. A small curved hæmostat would serve in place of the bone lever.

The incision was closed and the jaw supported for ten days.

SUMMARY

Two methods are described by which difficult dislocations of the jaw may be reduced when the classical methods fail.

GENERAL PRACTITIONERS' FORUM

THE POSTURAL DENSITY CHANGE OF URINE IN THE DIAGNOSIS OF EARLY CIRCULATORY FAILURE

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It has long been known that there is a diurnal rhythm in the renal excretion of water and its solutes (Winton, 1956). According to Lippmann (1952), the night urine should be less than 500 ml. in healthy subjects, averaging about 300 ml. Its specific gravity should be at least 1.018. The day urine will be of lower specific gravity, and greater volume: partly owing to diuresis following fluid consumption, and partly due to enhanced metabolic activity. Put at its simplest, the night urine is more concentrated than that passed by day.

INTRODUCTION

Various tests have been designed to draw conclusions from deviations from the above pattern and, when great accuracy is required, the volume of each specimen is recorded: but the greater the volume, the lower the specific gravity, and it is easier to deduce volume changes by measuring densities than it is to carry out a complete timed urine collection of the whole output. If the object is simply to detect nocturnal polyuria, an observation of a fall in specific gravity of the night specimen relative to the day specimen is sufficient. Elaborate comparison tests have been much used to determine renal efficiency: e.g. Mosenthal's, Volhard and Farr's, and Fishberg's tests (Todd *et al.*, 1953). Nocturnal polyuria has also been reported in Addison's disease due to loss of the diurnal rhythm of excretion (the Robinson-Power-Kepler test). These tests are complicated by volume measurements.

A new specific gravity comparison test is now described capable of detecting fluid retention, and the subsequent nocturnal polyuria, long before the resulting postural œdema becomes clinically evident. Such conditions as cardiac failure, hypertension, anæmia, toxæmia of pregnancy, and myxœdema give advance warning by causing insidious daily fluid retention—fluid which is expelled because of circulatory improvement when lying down. The resultant changed specific gravity pattern is easily shown. It is clear from intravenous infusion experience that the tissues can conceal about a litre of water in excess of their requirements without evident œdema, but this amount of water, added to the night urine, will dilute it three times over. Also, if this water is withheld from the day urine, this will be concentrated to about one-third so that the ratio between the night and day strengths will be powerfully affected by even small amounts of water retained by day and expelled by night.

The test is intended to be as simple as possible, so as to be of the greatest use to general practitioners whose time and facilities are limited, but whose task it is to detect disease early.

METHOD

The patient is asked not to drink after 5 p.m. unless thirsty, in which case he must report what he drinks. (The alternative ensures that an incipient uræmic coma will not be aggravated by dehydration.) Apart from the evening restriction, normal fluid intake is advised. The first urine specimen is collected on rising, and is added to any amounts that have been passed during the night. The second specimen is collected three hours later, and care must be taken not to confuse the two. Clear labelling is important. A sufficient sample of each specimen is brought to the doctor, and the specific gravities are determined at room temperature with an ordinary urinometer. The two results are expressed thus:—1018/1009 (+9), the figure in brackets being the 'postural density change index' (referred to hereafter as 'the Index') determined by subtracting the second value from the first. It indicates the degree of nocturnal concentration, and is approximately +10 in normal subjects.

In renal failure, the Index approaches zero as the uræmic polyuria increases, and the kidney's concentrating power fails. In circulatory failure, with its reversal of specific gravity pattern, a *negative index* is found. This is sometimes as marked as −10 in advance of clinical œdema, and such a negative index value is the earliest sign of circulatory failure.

THE INDEX IN HEALTH

Several estimations were made on a control (case 1) to see how far the index varied under different conditions, and with respect to evening drinks; and two other normal patients were studied in less detail (cases 2 and 3)—normal, that is, in their circulatory functions. All urine samples in the series were subjected to routine tests for protein, sugar and chlorides; but abnormal results only are reported.

Case 1.—A healthy male of 42 years produced the following results:—

After normal drinks (tea at 9 p.m., milk later, and tea at 7 a.m.; totalling 20 ounces (570 ml.)), rising at 8 a.m.	1022/1013 (+ 9)
Another morning under the same conditions	1018/1008 (+10)
Disturbed night (excitement); no evening tea	1015/1004 (+11)
After a very cold night	1020/1013 (+ 7)
Normal conditions again without restrictions	1019/1009 (+10)
Alcohol (3 whiskies) during evening, no tea	1019/1014 (+ 5)
One extra cup of tea at night	1013/1011 (+ 2)
Disturbed night (work) including tea-break	1013/1010 (+ 3)
Supper of milk and soup	1010/1008 (+ 2)
Digestion of breakfast delayed by stress	1018/1017 (+ 1)

Average value of index +8

The index would have averaged +10 if those instances where fluid was imbibed after 5 p.m. were excluded. On no occasion was the index negative.

Case 2.—A woman of 65 years, worried about her heart, had a blood pressure of 142/80 mm. Hg, a regular pulse of 80, and normal heart sounds. She had no dyspnœa, and no œdema of her ankles towards evenings. She could hold her breath for 31 seconds (Sebrasez's test). The urine density comparison test result was 1009/1005 (+4), without restricting fluids.

A diagnosis of mild endogenous depression was made, and recovery was uneventful. No organic disease was detected at any time.

Case 3.—A man of 71 years complained that his wind was failing. He had always been athletic, and was perhaps unduly concerned about his health, without being a hypochondriac. His blood pressure was 136/84 mm. Hg, and the pulse rate 92. No cardiovascular abnormality was found except for the tachycardia, and this varied from time to time in severity. He was able to hold his breath for 49 seconds. Urine tests gave 1017/1012 (+5) without restriction of fluids.

A diagnosis of nervous tachycardia, with no organic disease, seemed reasonable. Four months later he was still very fit for his age, and quite reassured by the investigation. (The double urine test had impressed him enormously, thus strongly supporting his doctor's reassurance.)

A LEADING AND MISLEADING CASE

Case 4.—This overweight woman of 69 years complained of dyspnœa on effort. She also had œdema of her ankles towards evening, and had noticed this for 10 or 20 years. Her blood pressure was 160/86 mm. Hg and the pulse rate 84. The heart sounds were normal. Urine tests gave 1009/1016 (−7), which was consistent with the œdema of ankles. A consultant physician was asked to elucidate the cause of the œdema, and the secondary nocturnal polyuria; and the patient's tight corsets were indicted. Since leaving them off, and reducing her nightly tea-drinking, she has had relief from her nocturnal polyuria, and her ankles are much less swollen in the evenings than formerly.

Case 5.—This lady was undergoing massive penicillin therapy for tertiary syphilis, and her cardiovascular system was investigated as a precaution although it was not clinically involved. Urine testing gave 1007/1010 (−3), but inquiry then revealed that she was drinking two glasses of water every night in the hope of washing the disease out of her system. Restriction of fluid before repeating the test gave 1008/1003 (+5), and other tests gave normal results.

After this experience, no negative index was accepted unless following fluid restriction. Her false negative was the only one noted in the six months during which the test was developed.

CONDITIONS PRODUCING A NEGATIVE INDEX

Myocardial weakness

Case 6.—A male aged 55 years, with chronic congestive heart failure, had been stabilized on digitalis, aminophylline, and limitation of activity, for some months. He could climb stairs if he rested halfway, and was up daily to sit about the house. Moderate œdema of the ankles occurred each evening. Although only five feet (152 cm.) tall, he weighed over 13 stones (82 kg.). Urine results were 1010/1020 (−10).

Case 7.—A male, aged 62 years, with known coronary disease, and also chronic bronchitis, complained of great breathlessness on slight exertion, but was able to hold his breath for 42 seconds. His blood pressure was normal (164/96 mm. Hg) and his pulse rate 88. His heart sounds were also normal. Urine results were, 1010/1018 (−8). He was asked to stay in bed for one day, and the urine test was then repeated, producing figures of 1011/1013 (−2). This pointed to the logical treatment of his case—to lie down for two hours daily after lunch—and on this regime he became much fitter, and remains so after three months.

Case 8.—This woman of 74 years had severe coronary deficiency associated with hypertension. Her pulse rate was 116, and blood pressure 240/94 mm. Hg. She had occasional swelling of the right ankle, but not the left one (probably determined by an old injury to her right leg). Severe dyspnœa and anginal pain occurred on walking. Sebrasez's test gave 5 seconds as her breath-holding time. The urine results were 1005/1011 (−6), improving to 1009/1009 (0) after one day in bed; and 1008/1008 (0) after three days on acetazolamide, 250 mg., every morning.

Case 9.—A male of 60 years, less severely affected than case 8 with coronary disease, had a blood pressure of 128/82 mm. Hg, a regular pulse of 84, and no œdema clinically. He was only moderately dyspnœic on effort, and was able to hold his breath for 27 seconds. Urine tests gave 1016/1020 (−4), but after one day in bed improved to 1025/1018 (+7). After being up and about for three days, but taking 250 mg. of acetazolamide every morning, his figures were 1020/1010 (+10) and he continues to do well after several months.

Case 10.—This man had anginal pain on effort, and slight swelling of the ankles in the summer, but not in cool weather. (There was no clinical œdema at the time of this assessment.) He was not troubled by breathlessness, and could hold his breath for 35 seconds. His blood pressure was 184/88 mm. Hg and pulse rate 92. Urine results were 1009/1012 (−3). He approximates to the borderline where œdema may or may not appear; nevertheless, his urine density reversal was marked, showing evident fluid retention by day.

Case 11.—This man, aged 58 years, also suffered from angina pectoris, but had no detectable circulatory failure. His blood pressure was 120/66 mm. Hg, and his pulse was regular at a rate of 64. He never had œdema, and required moderate effort to make him breathless or cause his pain. He managed 37 seconds comfortably in Sebrasez's test, and urine results were 1010/1005 (+5) without fluid restriction. He illustrates the well-known fact that occasional anginal pain does not necessarily imply circulatory deficiency under normal conditions.

Valvular incompetence

Case 12.—This woman of 36 years was not suspected of cardiac disease, but seemed pale, and came for 'a tonic'. Blood was taken for a hæmoglobin estimation, and she was asked to bring dual specimens of urine a few days later (mainly to satisfy her doctor's curiosity as to whether anæmia would produce a negative index). The hæmoglobin level was normal, but the urine result was 1010/1017 (−7), and clinical examination then revealed a slapping pulse, beating 108 times a minute, a blood pressure of 256/100 mm. Hg, and heart sounds indicative of aortic incompetence. Yet she had no complaint of œdema, dyspnœa, or of anything but her pallor. The Wassermann and Kahn tests were negative.

Hypertension

Case 13.—A woman of 67 years, much overweight, was treated for iron-deficiency anæmia with success, but was then discovered to have a blood pressure of 210/112 mm. Hg. Her pulse rate was regular at 88, and she developed swelling of the ankles towards evening each day. She was unable to hold her breath for more than 8 seconds, but was of poor mentality, and seemed afraid of the test. She complained of breathlessness only after moderate effort. Urine results were 1006/1010 (−4), and an improvement on acetazolamide was obtained to 1012/1013 (−1).

Case 14.—A woman of normal weight, aged 85 years, had had a previous cerebral thrombosis from which she had made a good recovery. On a small dose of reserpine her hypertension was controlled at 164/82 mm. Hg, with a regular pulse of 84. She never had œdema, and avoided breathlessness—'I never hurry, doctor!'—though she was fairly active for her age. Sebrasez's test gave 15 seconds only, and the urine test gave 1009/1011 (−2).

Case 15.—Another woman of normal weight, aged 70 years, had a blood pressure of 190/116 mm. Hg, reducing to 178/88 mm. Hg on a maintenance dose of reserpine. She had no œdema, and to the question, 'Do you get breathless on effort?' she replied: 'Not really, doctor'. She could hold her breath for 25 seconds without discomfort. (She had originally complained of breathlessness on effort, a symptom dispelled when her pressure fell to normal levels.) Urine tests gave 1020/1009 (+11) and she has continued to do well. Unfortunately, the urine comparison test was not in use until after she had become stabilized, so that an earlier comparison is lacking.

Case 16.—Symptom-free hypertension was found by chance in a woman of 70 years. Her blood pressure was 196/118 mm. Hg, and the pulse rate 88 and regular. She had no œdema, and no complaint of undue breathlessness. She could hold her breath for 57 seconds. Her urine results were 1019/1010 (+9), and she has remained well without any special treatment.

Possibly the urine test described will help to differentiate simple physiologica hypertensives such as this one from those requiring active treatment.

Myxœdema

Case 17.—A woman of 52 years, weighing 165 lb. (75 kg.) and 62 inches (157 cm.) tall, complained of loss of energy and of her hair falling out. She was depressed and tearful. She also complained of headaches and numb feelings, and general irritability. Her medical history was of several attacks of acute cystitis, at intervals of several months, each responding to treatment with one or more antibiotics. She had gained weight in recent years. On examination she was found to have typical alopecia areata associated with the places where she felt numb, and had headaches. Her blood pressure was 156/100 mm. Hg, the pulse 80 and regular, and the erythrocyte sedimentation rate (Westergren) 5 mm./1 hr. Urine results were 1013/1011 (+2).

She was treated with chlorpromazine, 100 mg. daily, for three weeks with no improvement, and her alopecia extended. A blood cholesterol at this time was 240 mg. per 100 ml., and thyroid extract was given at the rate of 3 grains (0.2 g.) daily. The chlorpromazine was stopped. After one month she was much improved. Her headaches and numb feelings had vanished, and her hair was growing vigorously where the alopecia had been. The pulse was still 88, and there had been no weight loss. The blood cholesterol was now 222 mg. per 100 ml. A urine test gave 1010/1017 (−7) without fluid restriction, but repeating it, with due control, gave 1008/1006 (+2). On this last occasion she complained of slight swelling of the ankles towards evening, and the pulse rate had risen to 96. The thyroid extract was therefore reduced to 1 grain (60 mg.) daily, and after a further two weeks she was tested again. The results were then 1014/1008 (+6), and all clinical tests gave normal results. She appeared to be very fit, and had lost 5 lb. (2.25 kg.) in weight without dieting. She spontaneously remarked: 'I haven't been so well for years', and she continues to enjoy apparently blooming health on 1 grain (60 mg.) of thyroid daily.

Case 18.—This woman, aged 66 years, of normal weight, complained of chest discomfort on effort. She had no œdema; the blood pressure was 158/86 mm. Hg, and her pulse rate 92 and regular. She seemed very nervous, and it was not possible to do a satisfactory Sebrasez's test. A urine test showed 1009/1008 (+1), and a timed urine collection showed that she was producing 750 ml. of urine at night of specific gravity 1012. The blood urea was 50 mg. per 100 ml. No urinary casts and no crystals were observed microscopically, but pus cells and occasional red blood cells were reported. Proteinuria tests were repeatedly negative. No evidence of renal disease was found. Her appearance suggested myxœdema, and she was therefore given 2 grains (0.12 g.) of thyroid extract daily. After a few days she felt much better, and her urine comparison test gave 1011/1002 (+9). Her pulse remained at 92, and she weighed 1 lb. (450 g.) lighter. A second blood urea again gave 50 mg. per 100 ml. She has remained well on thyroid, without any complaint of chest discomfort, for two months; and no circulatory disease has been found.

Varicose veins

Case 19.—This plump woman of 50 years had severe varicose veins, and her ankles swelled up daily. She worked in a shop, standing all the time. Her blood pressure was 174/86 mm. Hg and the pulse rate 96. She had no dyspnœa on moderate effort, and was able to hold her breath for 53 seconds. Her sedimentation rate (Westergren) was 11 mm./1 hr., and the hæmoglobin level (Sahli) 92 per cent. Urine tests gave 1020/1025 (−5), which was no doubt due to her localized œdema of ankles.

Case 20.—This very active woman of 38 years had marked varicose veins. She was not overweight; the blood pressure was 164/86 mm. Hg and the pulse rate 92. She complained of swelling of the ankles each evening, and slight breathlessness on effort. She could hold her breath for 33 seconds. The hæmoglobin (Sahli) was 102 per cent. Urine tests gave 1008/1006 (+2). Proteinuria was absent, and the blood urea was 39 mg. per 100 ml. Repeating the tests gave 1015/1012 (+3). She continues to remain well, except for her varicose condition, after two months.

Obesity

Case 21.—A man of 60 years, 66 inches (168 cm.) tall, and weighing 299 lb. (136 kg.) was investigated. His blood pressure was 166/90 mm. Hg and his pulse rate 84, with normal heart sounds (so far as they could be heard through the fat). He had no œdema towards evening, and complained of breathlessness only after moderate effort. He could hold his breath for 32 seconds. Urine tests showed results of 1015/1020 (−5), improving to 1015/1012 (+3) after one day in bed. He is an illustration of the circulatory load imposed by obesity, even though clinical signs are lacking when normal tests are applied.

DISCUSSION

No cases of *toxæmia of pregnancy* have been available for study during the six months in which the test has been developed, but it seems likely that the urine comparison test will give the earliest possible indication of fluid retention from this cause, long before œdema of the ankles is noticed. Nocturnal polyuria may well be the earliest sign of deviation from normality in the toxæmic mother. If so, routine density comparison tests during pregnancy will become important.

Anæmia was also unrepresented during the period reported, and, as in the case of toxæmia, it is likely that density reversal will precede œdema of the ankles. This also applies to any *nutritional deficiency* state causing œdema in its well-developed forms.

Diabetes and uræmia may well be discovered by doing urine comparison tests in obscure illnesses. They are included here to point out that they are associated with water loss, which leads to dehydration of the tissues and thirst; but polyuria due to circulatory failure is accompanied by excess fluid in the tissues, and thirst is not a feature. In uræmia, also, lies the main reason for having two specific gravity determinations rather than one measured nocturnal specimen for detecting nocturnal polyuria. The failure of the kidney to vary specific gravity according to the needs of the moment is suggested when the index is near zero. A marked positive or negative value depends upon a kidney able to concentrate or dilute the urine when required.

Finally, the dual test requires only a simple procedure and is inexpensive. It moves forward the frontier of clinical detection and measurement of early circulatory failure in the place where this is most desirable—the

general practitioner's consulting room. It is certainly not a hospital test, except perhaps on outpatients who are ambulant. Its significance in prognosis will be more evident in a few years' time.

This article was awarded the second prize in the 1957 competition for the 'Benger Prizes for original observations in general practice', adjudicated by the College of General Practitioners.

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TWO UNUSUAL DISEASES SEEN IN GENERAL PRACTICE IN ONE WEEK

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During his daily round a general practitioner faces many problems, the bulk of which are common and minor complaints but nevertheless packed with interest. From time to time, however, he is confronted with one of the more unusual diseases or syndromes and given the opportunity for their diagnosis and management. Their coming gives new insight into the mysteries of disease, making it obligatory on us all to give them our best thought and attention. In this short note I describe two patients in whom such syndromes occurred in my practice within the space of three days.

DISSECTING ANEURYSM OF THE AORTA

The first was a male, 71 years old, whose emergency call I answered in the late evening of May 11, 1957.

He had developed a slight pain in the precordium, which cleared in a few minutes, only to spread into the left leg. There it was very severe, though associated with a numb sensation. He was well known to me and his rather agitated manner in no way unexpected. Examination revealed the left leg to be cold and pale below the knee with an easily palpable femoral pulse, but no pulsation in the distal arteries. There was diminished sensation to pin prick and the tendon jerks were absent. No abnormalities were detected in the right leg and the pulses of the upper limbs, head and neck were readily perceptible. There was no evidence of shock, the blood pressure being 200/110 mm. Hg and the pulse rate 90 per minute. A moderately loud systolic murmur could be heard in all areas of the precordium (which had been noted two years previously) but the heart was not clinically enlarged. A gross kyphosis of the lower thoracic spine completed the abnormalities of the trunk; and the well-known rhinophyma and cataract of the right eye were once more observed. No albuminuria was present and a subsequent white blood cell count was 17,200 per c. mm.

A diagnosis of thrombosis of the left popliteal artery was made, morphine sulphate, ¼ grain (16 mg.), administered, and he was admitted to hospital the same evening. There anticoagulant treatment (phenindione) was instituted and his progress watched. The following morning (12 hours after the incident) the left femoral pulse was found to be absent although the leg itself appeared to have more colour. The pain was much easier. Over the next few days no change was noticed in the pulses

though colour changes in the leg suggested an early gangrene. On the morning of May 20, three days after the onset, he collapsed suddenly and died. Necropsy was performed one day later and showed a dissecting aneurysm of the aorta which had started just above the aortic valves and spread all the way along the aorta, the left common iliac and left femoral arteries to just below the inguinal ligament. Rupture had taken place just above the diaphragm into the pleural sac, which contained about 2½ pints (1.5 litres) of clotted blood. The heart was not enlarged.

Comment.—Dissecting aneurysm can present innumerable clinical pictures, each depending upon which artery is occluded. Had I taken more notice of the slight chest pain perhaps a confident ante-mortem diagnosis could have been made (which is perhaps a mild indictment against knowing our patients too well). Dissecting aneurysm is not common, the diagnosis being made usually at a coroner's necropsy. Dr. R. Leader, the Medical Officer of Health for Ipswich, tells me that during the twelve months, February 1955 to January 1956, it was responsible for seven deaths (six certified by the coroner) in his county borough of some 105,000 people. Rupture back into the aorta may be life-saving and only revealed at a later post-mortem examination, and one cannot help feeling that many such cases are never diagnosed. The extent of dissection present in this case is unusual, the extravasation commonly stopping after a few centimetres along the main branches of the aorta.

RAMSAY HUNT SYNDROME

Fear of impending dissolution was again the cause of an emergency call at midnight on the same day as the necropsy on the patient already described.

A male patient, 66 years old, had for three days had pain in the pinna, mastoid region and angle of the left jaw associated with sores on the pinna. No pain had been felt in the throat. Immediately preceding the call he had suddenly noticed a weakness and numbness of the left face and had come to the catastrophic diagnosis of 'a stroke'. Examination revealed a complete paralysis of the left face of the lower motor neurone type (fig. 1). Taste, though difficult to test, appeared to be impaired over the anterior two-thirds of the left side of the tongue. There was no diminution of sensation in the trigeminal region, nor were any other abnormal physical signs found on examining the central nervous system. Two granulating areas could be seen on the pinna: one in the fossa triangularis and one in the concha (fig. 2). No other vesicles were noticed and the ear drum appeared normal. There was slight œdema of the whole area. A temperature of 100°F. (37.8°C.) was noted, which persisted four days. Full examination showed no other abnormalities.

A short course of intramuscular penicillin, 500,000 units twice daily, was given as it was thought that the paralysis might be caused by the surrounding inflammatory œdema. There was no improvement. Reports of the value of cortisone and corticotrophin (Sheard and Felder, 1955) in the Ramsay Hunt syndrome prompted me to give cortisone a short trial. This was started on the 14th day of the illness in a dosage of 200 mg. daily for three days, followed by a gradual reduction over the next four days. There was no response. On the 36th day of the illness he was referred to the physiotherapy department and given short-wave diathermy and labile galvanism thrice weekly for three months. At the same time a suitable splint was made by a dental surgeon to hold up the angle of the mouth. When last seen, six months after the onset of the illness, there was no movement of the facial muscles. Nevertheless there had been some contraction of the muscle fibres so that the corner of the mouth no longer drooped, thus giving a satisfactory cosmetic result.

Comment.—This patient's lesion fits admirably in the syndrome described by Ramsay Hunt, the skin involved being confined to the pinna. At no time

was there any involvement of the skin supplied by the Gasserian or cervical ganglia. The vesicles seen, though infected, were quite typical of those to be found in cases of herpes zoster. This fact associated with the presence of pain preceding the onset of the lesion suggests that this condition is a herpetic infection. The site of the lesion in the Ramsay Hunt syndrome has

FIG. 1.—Left facial paresis in the Ramsay Hunt syndrome.

FIG. 2.—Vesicular eruption in the Ramsay Hunt syndrome. Photograph taken eighteen days after onset.

been the cause of much debate and it is probable that there are many sites producing a similar picture, though with the vesicles in different dermatomes. The cause of the facial paralysis in some of these cases may well be due to the surrounding œdema in the area, causing compression of the nerve in the stylo-mastoid foramen. Sensory fibres have been described in the facial nerve and there seems no reason, in this case, why the lesion cannot be placed in the geniculate ganglion. The failure of cortisone to improve the facial paralysis is probably due to the fact that it was given too late, when degeneration of the nerve had already occurred.

The syndrome is rare: only 12 cases, for instance, being seen in a period of five years at a large otological unit in Manchester (1954). This rarity does not make the diagnosis difficult nor its management beyond the scope of the general practitioner. A full review of the condition, including theories as to the site of the lesion can be found in the report of a discussion on the subject held at the Royal Society of Medicine in 1954 (Harrison, 1954).

SUMMARY

This brief account of a patient suffering from dissecting aneurysm of the aorta and of a patient suffering from the Ramsay Hunt syndrome is presented to remind us all that, under the National Health Service, as before it, the family doctor can still remain the complete physician.

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A CASE OF SUBACUTE BACTERIAL ENDOCARDITIS AT SEA

By A. M. PORTER, M.B., B.S., D.R.C.O.G.
Ship's Surgeon

Whenever a large liner leaves port, she carries a complement of crew and passengers, which numerically equals the size of an average general practice. As in any practice, minor maladies will form the greater part of the surgeon's work, but almost certainly during the course of the voyage there will be one or more cases which will give rise to much anxiety, and involve grave decisions. Such was the following case.

HISTORY

The patient, a spinster of 46 years, was travelling to Australia. On the third day of the voyage she reported to the ship's surgery, complaining of an 'influenza-like' illness for two weeks and swelling of her ankles for two days. She thought that something had been wrong with her heart all her life, but she had been symptomless and able to indulge in normal activities. There was no history of rheumatic fever.

CLINICAL FINDINGS

General examination revealed a host of physical signs. A pronounced mitral flush overlay a 'café au lait' skin; she appeared anæmic and mildly cyanotic and there was early clubbing of the fingers. A slightly raised jugular venous pressure and pitting ankle œdema suggested mild cardiac failure, but the pulmonary bases were clear. The heart was enlarged with an intense thrill over the base. There was a correspondingly loud basal systolic murmur, maximal in the 2nd right intercostal space and referred up the carotid arteries; no diastolic murmur was heard. A careful search was made for splinter hæmorrhages and Osler's nodes but none were found, nor was the spleen palpable. A catheter specimen of urine contained no blood or pus.

MANAGEMENT

She was admitted to the ship's hospital for observation. Although initially apyrexial, that night her temperature rose to 100.2°F. (38°C.), and a tentative diagnosis of subacute bacterial endocarditis superimposed on aortic stenosis was made. The ankle œdema subsided rapidly with one injection of mersalyl but for the time being antibiotics were withheld. Over the next few days it became clear that she was running a hectic remittent temperature of up to 103°F. (39.9°C.), which was not associated with rigors. A careful search for a focus of infection was negative. It was at this point that a chance reading of an article by Hobson and Juel-Jensen (1956), underlining the importance of carious teeth in the etiology of subacute bacterial endocarditis due to *Streptococcus viridans*, seemed to have an immediate relevance. An examination of the patient's teeth proved them to be in an advanced carious state and consequently suspicion hardened on the diagnosis of subacute bacterial endocarditis.

It remained to take blood cultures before starting treatment and without delay some agar and broth were obtained at Las Palmas.

The sterilization of the plates and syringes presented a problem, until it was realized that the large vegetable steam cooker in the galley could achieve a pressure of 7 lb. per square inch and made quite an efficient autoclave. The top of an electric refrigerator made a useful incubator. There was a temperature gradient from the back to the front down which each day the plates were moved, as the ship passed into tropical waters and the air temperature rose. Blood cultures were taken on two consecutive days with the usual precautions and at the height of the fever. They were passed through broth and plated on to agar. The broth was then refrigerated and sent with the patient when she was eventually admitted to hospital at Perth.

It was disappointing that both of our plates were sterile and that no organism was ever subsequently cultured from the broth.

Four days after her admission to the ship's hospital, systemic penicillin was started, 0.8 mega unit of a mixture of procaine and crystalline being injected twice daily. The response was immediate and dramatic, and for the first twenty-four hours she was apyrexial, but thereafter she commenced a low-grade intermittent fever associated with tachycardia. During the second week of her admission the blood pressure had dropped from an initial 100/70 mm. Hg to only 85/70 mm. Hg. The hæmoglobin had fallen from 64 per cent. to 50 per cent. (Gowers) and the pulse rate showed a steady and ominous rise. It seemed prudent to double the dosage of penicillin to 1.6 mega units twice daily. A slow transfusion of packed red cells was also considered, until it was learnt that she held strong religious scruples against blood transfusions, the very mention of this subject evoking great distress.

At this stage it was decided not to land her at Capetown but to take her to Australia. In retrospect I am certain that this difficult decision was the correct one. Against the many advantages a large hospital offers, must be offset the distress caused to a patient, often timid and impecunious, who

finds herself in a strange land, many thousands of miles from her nearest relatives and friends.

As the illness entered the fourth week it was noticed that the cardiac sounds had changed in character and that there was now a blowing diastolic murmur at the apex and a variable pleuro-pericardial rub to the left of the lower sternum. There were still no specific signs of subacute bacterial endocarditis. Despite this, the prolonged fever and changing cardiac signs left little doubt as to the diagnosis and also the inadequacy of the antibiotic therapy. Once more the dosage of penicillin was increased to 1.6 mega units thrice daily, and the reluctant decision was made to add streptomycin 1 gramme twice daily by injection. It had been hoped to leave the decision of additional antibiotic therapy to the hospital to which she was discharged, but her critical condition made this impossible.

Six days later, when at last there appeared to be a response to treatment, she was landed at Fremantle and admitted to the Royal Perth Hospital. On arrival at hospital the dosage of penicillin and streptomycin was increased still further, but two days later the long threatened attack of acute pulmonary œdema materialized. Surviving this, she agreed to a small and very slowly given transfusion of packed blood cells. By now she was apyrexial, but an ever-mounting blood urea foretold the outcome and she died in cardiac failure ten days after leaving the ship, in the sixth week of the illness.

POST-MORTEM FINDINGS

At necropsy a calcified aortic stenosis was found and thought to be congenital in origin, although the existence of this entity is not universally accepted. An acute and subacute endocarditis involved the aortic valve and extended up into the aorta and down towards the normal mitral valve. One infarct of the spleen was found but there were none of the lungs and kidneys. Post-mortem cultures were taken from the heart and spleen, but both were sterile.

CONCLUSION

In retrospect one must regret a lack of boldness in raising the dosage of penicillin following the initial relapse and an over-conservative reluctance to introduce streptomycin. Although antibiotics have completely changed the prognosis of this disease, their correct use still poses many problems and for the writer this case was not without its lessons.

I am indebted to Dr. I. Corbett, the medical superintendent of the shipping line, for permission to publish this case; to Mr. L. Goodman, F.R.C.S., ship's surgeon, for his kind help and advice; to Dr. Broca, The Royal Victorian Hospital for Seamen, Las Palmas, for making available the agar and broth, and to Dr. C. Fortune, the Royal Perth Hospital, for a detailed follow-up.

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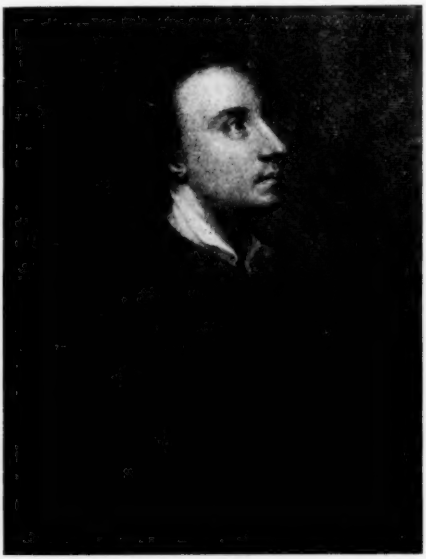
POETIC DOCTOR

MARK AKENSIDE, M.D., 1721-1770

By BRIAN HILL

MARK AKENSIDE hailed from Newcastle upon Tyne. His name was actually 'Akinside' and his early letters are signed in this fashion. He altered the spelling when he moved south to London, perhaps because the name Akinside for a doctor provoked crude puns from those who fancied themselves wits. He was the son of a butcher and came of dissenting stock on both sides of his family. It was said that in later life he was ashamed of his comparatively humble beginnings and tried to conceal the facts of his parentage; physically, however, he could not escape so easily from the butcher's shop for he carried its mark about with him. In his childhood a cleaver had accidentally fallen on his foot and left him with a permanent limp.



Mark Akenside, M.D., 1721-1770

EDINBURGH AND LEYDEN

The boy was educated first at the free school in Newcastle and afterwards at a private school kept by a dissenting minister. He achieved print in his schooldays, for the *Gentleman's Magazine* published several of his attempts at verse before, at the age of eighteen, he left his native city for Edinburgh to study for the Presbyterian ministry. Young Akenside soon realized, however, that he had no vocation for the church; he transferred himself to the medical school. 'Whether', commented Doctor Johnson acidly, 'when he resolved not to be a dissenting minister, he ceased to be a dissenter, I know not. He certainly retained an unnecessary and outrageous zeal for what he called and thought liberty'.

Akenside was, in fact, a strong Whig with more than a leaning towards republicanism. He even contemplated a political career at one time. While at Edinburgh he joined the Royal Medical Society and spoke regularly at

their meetings. Indeed, his fellow-students seem to have thought him more fitted for the rough and tumble of parliamentary debates than for the consulting room and surgery. Such dreams, however, faded like so many of the aspirations of youth. Akenside completed three years' study at Edinburgh without apparently taking a degree, and returned to his family at Newcastle.

In Scotland, however, he had made the beginnings of a friendship which was to have a powerful influence on his future career. He met Jeremiah Dyson, 'a young gentleman of fortune', as the eighteenth century agreeably described any man who enjoyed an unearned income, and a firm and lasting friendship sprang up between the two young men. Dyson, who was studying law, spent the winter of 1743 in Leyden, and it was probably his recommendation that sent Akenside to take his medical degree in that city.

It was at this time, too, that he began to make his poetical reputation. Eighteenth-century readers liked long poems and the young doctor's offering was certainly in the fashion, for it was a didactic poem in blank verse and three books entitled 'The Pleasures of the Imagination'. He submitted the manuscript to the well-known publisher, Dodsley, asking the rather large sum of a hundred-and-twenty pounds for it. Dodsley, it is said, asked Alexander Pope to have a look at the poem and see what it was worth. The report was favourable. Pope 'advised him not to make a niggardly offer; for "this was no everyday writer" '. The work was published at the beginning of 1744 and met with an instantaneous and most gratifying success. Nevertheless Akenside did not abandon his medical career. In May of the same year he received his degree of Doctor of Physic and was able to leave Holland for England.

NORTHAMPTON

The question now was where should he attempt to set up a practice. Northampton, he gathered, was a town in which a physician just starting his career might expect to find patients, and to Northampton Akenside betook himself. It was not long, however, before he realized that a newcomer could not hope to compete with another doctor who was already firmly entrenched in the town. Some idea of the cut-throat medical competition of the time can be gathered from the writer of a letter to the *Gentleman's Magazine* after Akenside's death. This correspondent says that, 'this contest for the physical business at Northampton, though unsuccessful on the part of Akenside, had for some time been supported by him with extraordinary violence . . . not only a fair and open struggle of medical hostilities, but every art and every exertion, personal abuse and private insinuation, had been used to usurp Doctor Stonehouse's professional emoluments, and oust him from his established settlement'.

At the end of a few months Akenside had to admit defeat in spite of having, as Doctor Johnson phrased it, 'deafened the place with clamours of liberty'.

He resolved to try his luck again at Hampstead, and it says much for his Northampton rival's magnaminity that Doctor Stonehouse gave him a letter of introduction and recommendation. Perhaps he was too glad to get rid of his competitor to harbour feelings of resentment. But if Akenside's stay at Northampton achieved no medical success, it produced what is generally judged to be his best piece of writing: that powerful and brilliant satire 'An Epistle to Curio'. The subject of this work was William Pulteney, Earl of Bath, Sir Robert Walpole's political opponent. Macaulay said of this poem that if the author 'had left lyric composition to Gray and Collins and had employed his powers in grave and elevated satire, he might have disputed the pre-eminence of Dryden'.

HAMPSTEAD

At Hampstead, Akenside and Dyson set up house together. The latter had obtained by purchase the office of Clerk to the House of Commons—he is said to have paid his predecessor six thousand pounds for the job—and thereupon bought a villa at North End, Hampstead. Unfortunately, Akenside, instead of conciliating the Hampstead gentry and their wives who might have come to him as patients, allowed himself to air his views on liberty and other subjects, became involved in acrimonious arguments and too plainly showed his contempt for those who differed from him. Hampstead social circles took their revenge on the haughty physician by sneering at his pretensions to gentility. Patients were lacking, but Dyson once more came to the rescue. The Hampstead villa was sold and Akenside was settled in 'a small but handsome house' in Bloomsbury Square. So London, which was, as a contemporary put it, 'the proper place for a man of accomplishments like his', became Akenside's home for the remainder of his life. He made two further moves within the confines of the metropolis: first for a short time to Craven Street, and finally to a house in Burlington Street. Moreover, Dyson generously made over to his friend a sum of money sufficient to provide him with a reasonable annual income. It is stated to have been three hundred pounds a year, but may have been more. At any rate it enabled Akenside to keep his own chariot and enjoy every comfort.

He was now twenty-seven years of age. He wrote little more poetry, though he acted for a time as editor of and contributor to Dodsley's magazine, *The Museum*. From this time onwards his efforts were concentrated on success in his other profession. He sought in every way to build up a practice and increased his reputation by publishing from time to time treatises on medical subjects. His 'De Dysenteria Commentarius', produced in 1764, was considered to have 'entitled him to the same height of place among the Scholars as he possessed before among the wits'.

THE CONSULTANT

In 1753, Akenside was granted a doctor's degree by the University of

Cambridge and elected a Fellow of the Royal Society; the following year he became a Fellow of the Royal College of Physicians, to which body he lectured on more than one occasion. In 1759, he delivered the Harveian Oration before the College and in the same year was appointed assistant physician to St. Thomas's Hospital, becoming principal physician two months later. He does not seem to have been very popular, however, either with the patients or with the staff. One of the surgeon-dressers at the Hospital in Akenside's time found him 'the most supercilious and unfeeling physician that he had hitherto known. If the poor affrighted patients did not return a direct answer to his queries he would instantly discharge them from the hospital. He evinced a particular disgust to females, and generally treated them with harshness'.

This witness, who winced at Akenside's rough treatment of his patients and wondered to see him preceded through the hospital by two porters keeping the patients at a distance, has also left us a picture of the doctor. 'One leg of Dr. Akenside', he says, 'was considerably shorter than the other which was in some measure remedied by the aid of a false heel. He had a pale strumous countenance, but was always very neat and elegant in his dress. He wore a large white wig, and carried a long sword'. In general his acquaintances agreed that Akenside's manners were marred by stiffness and pomposity. 'He looked', said one, 'as if he never could be undressed'; whilst another noticed that the doctor hated to see anyone smile or look cheerful in the presence of an invalid, a remark which hardly suggests that Akenside had a good bedside manner. Finally, an actor acquaintance hit him off in an epigram: 'Akenside, when he walked the streets, looked for all the world like one of his own alexandrines set upright'.

The poet was obviously not a very likeable man, although in the company of his friends he could display a genial erudition. But even with his intimates he was disputatious and his inability to take a joke against himself landed him in some ridiculous quarrels. One of these was with a fellow-physician, Dr. Hardinge, a bluntly outspoken individual. The scene was Hardinge's dining-room and the subject on which the two men fell out was, appropriately enough, a bilious colic. The argument became heated, erupted into invective and, in spite of the efforts of his hostess to keep the peace, the angry guest ordered his carriage, vowing never to set foot in the house again. Another quarrel, equally absurd, arose out of a dispute with a little misshapen lawyer named Ballow. Akenside, angered at some remark of the other's, demanded an apology and when none was forthcoming sent him a challenge. The lawyer showed little inclination to use his sword and kept hidden in his lodgings until mutual friends induced the doctor to abandon his warlike manœuvres. An unkind comment on the affair was that it was settled by the obstinacy of both opponents: one refusing to fight in the morning, the other in the afternoon.

Akenside fell foul, too, of the doctor-writer, Tobias Smollett, but the

latter had the best of it, for he caricatured his enemy cruelly in his novel 'Peregrine Pickle'.

THE ROYAL PHYSICIAN

As is not uncommon, the advancing years damped down the fires of Akenside's youthful politics. Indeed, the glowing radicalism of his twenties burned so low that he was accused by his Whig acquaintances of deserting them for the opposite party. In 1761, he accepted the position of one of the physicians to Queen Charlotte, the young bride of George III, a step which led many people to believe that he had betrayed the cause of liberty and had become a convert to the Tory reactionaries.

The last years of his life Akenside spent in extending his medical practice and in revising the work that had first made him known to the world, 'The Pleasures of the Imagination'. He was an incorrigible improver—as he fancied—of his own work. He turned his 'Epistle to Curio' into an ode—and largely spoiled it in so doing; and he continually tinkered with his other poems, generally not to their improvement. He did not live, however, to complete his task of surveying those almost limitless prairies of blank verse that had been the familiar and loved homeland of his youth. While he was still working on the third book he was taken ill with a sudden 'putrid fever'. Possibly the disease was typhoid. Its results were quickly fatal; Akenside died at his house in Burlington Street on the 23rd of June, 1770; he was in his forty-ninth year.

After the funeral—the poet is buried in St. James's Church, Piccadilly—Dyson took charge of his dead friend's books and papers. Two years later he published a handsome memorial volume of Akenside's complete works.

'POETICAL BUT NOT A POET'

Akenside is, it must be confessed, rather a disappointment as a poet. It might be said of him, as was said of another eighteenth-century versifier, 'the gods made him poetical, but not a poet'. He had a genuine love of beauty, he was a good classical scholar, he admired Milton, Spenser and Shakespeare; but when he came to translate his inspiration into words something is lacking. 'He belongs to a class of poets', said Professor Saintsbury, 'who are plaster rather than marble, photograph rather than picture, pinchbeck rather than gold or even copper'. Doctor Johnson's judgment is even more damning. 'One bad Ode', he thundered, 'may be suffered; but a number of them together makes one sick'. And when Boswell one day mentioned Akenside's most famous work, the Doctor, in a burst of candour, confessed that he had never been able to read it through. Most modern students of eighteenth-century literature would make the same admission.

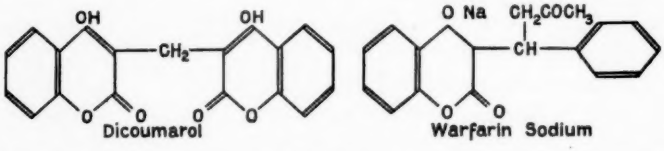
CURRENT THERAPEUTICS

CXXVII.—WARFARIN: A NEW COUMARIN ANTICOAGULANT

By HERBERT S. SISE, M.D.

From the Tufts Medical Services and Anticoagulant Laboratory, Boston City Hospital, and the Department of Medicine, Tufts University School of Medicine, Boston, Mass.

ALTHOUGH many modifications of coumarins and indanediones have appeared since the original discovery of dicoumarol, improvements over the original preparation have not been outstanding. One preparation has appeared, however, which is worthy of attention. Developed in the laboratories of Link, the discoverer of dicoumarol, it was called successively anticoagulant -42, warf-42, and finally warfarin in recognition of the major financial support from the Wisconsin Alumni Research Foundation (WARF). The funds of WARF are derived in a small part from the proceeds of the commercial manufacture of dicoumarol. In surveying the many 3-substituted-4-hydroxy-coumarins synthesized in Link's laboratories, Scheel and Ballou found this to be the most potent of all the compounds



tested. It was fifty times more lethal to rats and about twice as rapid in this respect as dicoumarol. The structural relationship to dicoumarol is shown in fig. 1. Being highly soluble as the sodium salt and effective in small amounts, it was first used as a rat poison. Human use as an anticoagulant was first reported in 1953. Approximately 1000 cases have been reported to have received the drug since then without toxic effects other than bleeding.

The property which distinguishes warfarin is its high degree of solubility as the sodium salt. It can be dissolved in small amounts of saline solution and be given intravenously, intramuscularly, or even rectally. The high degree of solubility may also be responsible for rapid and complete absorption from the gastro-intestinal tract. For instance, the oral and intravenous dose are the same, and the effects of an oral dose appear almost as soon as the effects of an intravenous dose, indicating rapid and complete absorption. In the experimental animal, absorption through the gastric wall has been shown to take place.

DOSAGE

Initial dose.—The initial dose recommended by most observers is 75 mg. for

the average person. If the original prothrombin time is prolonged some recommend the use of a smaller initial dose, namely, 50 to 60 mg.; others feel that the smaller dose may be preferable in all patients. On the average, an initial dose of 75 mg. will be adequate in about three out of four patients. The fourth patient will show either an insufficient or an exaggerated response. The initial dose may be given orally but, if the patient is vomiting or comatose, it may be convenient to use the intravenous route. Following either route, the prothrombin time first becomes prolonged in about twelve hours, usually reaches a range of 25 seconds in twenty-four hours and a peak effect at thirty-six to forty-eight hours. The effect persists for four to seven days.

Maintenance dose.—The maintenance dose is started only after the prothrombin time begins to recover in the direction of normal. The average individual requires somewhat less than 10 mg. a day, but there is a wide variation from patient to patient, some requiring as little as 2 mg. a day and others as much as 30 mg. daily. Two types of maintenance schedules have been used. One, the intermittent dose method, relies on the giving of a fairly large dose and then waiting for the prothrombin time to return towards normal before the next dose. The second and more popular method depends upon the giving of a daily maintenance dose which is adjusted either upwards or downwards according to the trend of the daily prothrombin time. There are certain theoretical advantages in the latter method.

COMPARISON WITH OTHER ANTICOAGULANTS

There is general agreement that warfarin is much more rapid in onset of effect than dicoumarol. Also, it is quite obvious that a 'steady state' is reached sooner with warfarin than with dicoumarol. Once this 'steady state' is attained, there is more success in keeping the patient within prescribed limits with warfarin than with dicoumarol, but opinions differ regarding how great the difference is. For instance, Shapiro *et al.* (1958) met with nearly equal success in treating 100 patients with warfarin as in treating 100 patients with dicoumarol. There were twice as many escapes with dicoumarol but less hypersensitivity. Nicholson (1957), on the other hand, indicated that much more success was achieved with warfarin: there were four times the escape periods when dicoumarol was used compared with warfarin. In comparing warfarin with phenindione, Kerrin, Guidot and Wilhelm (1957) indicate that the speed of effect is identical. They show, however, that the patients on warfarin were out of control about half as often (10.1 per cent. of the time) compared with patients treated with phenindione (19.7 per cent. of the time). Comparison with ethyl biscoumacetate has not been done formally. It seems likely, however, that the two are similar in speed of onset but that the duration of effect of warfarin is much longer.

MECHANISM OF ACTION

Warfarin exerts its anticoagulant effect by inhibiting the synthesis of

prothrombin, factor VII, Stuart factor, and Christmas factor in the liver. The prolongation of prothrombin time in the early part of treatment is largely due to a lack of factor VII, not of prothrombin or any of the other factors. Consequently, the prolongation of prothrombin time is in essence a reflection of the disappearance curve of factor VII from the plasma. The disappearance of prothrombin, Stuart factor and Christmas factor occurs later and is not associated with any further change in the prothrombin time. Observations in our laboratory indicate that the disappearance rate of all these factors is not dissimilar when warfarin is compared with phenindione. Thus, it may be said with some assurance that the effect of warfarin is no different from that of any of the coumarin types of anticoagulant.

Effect of vitamin K.—There are two forms of vitamin K found in nature. One is a crystalline product originally isolated from fish meal. This is a water-soluble naphthaquinone which was later termed vitamin K_2. The other is a non-crystalline, more potent, oily product from alfalfa which has been called vitamin K_1. Many synthetic quinones and naphthaquinones with vitamin K type properties have been formulated which behave like the less potent water-soluble vitamin K_2: e.g. menaphthone, 'synkavit'. The affinity of vitamin K_2 for the liver system, which synthetizes the four coagulation factors already mentioned, is less than the affinity of the coumarins to this system. Consequently, the coumarins can dominate the system and inhibit the synthesis of these products. Vitamin K_1, however, appears to have a greater affinity for the system so that its administration can overcome inhibitory effects of coumarins. The great variation in sensitivity to anticoagulants may have some relation to the vitamin K_1 available to the liver. Certainly, administration of vitamin K_1 can increase the resistance to all coumarin-type drugs. In this respect warfarin is no exception. By the same token, however, the effect of warfarin can be rapidly reversed by vitamin K_1. This property is very useful in the treatment of overdosage, particularly if there is bleeding. As with other anticoagulants, the water-soluble vitamin K_2 or similar compounds have very little or no effect.

If bleeding or an excessively long prothrombin time is encountered, vitamin K_1 (phytonadione) should be used to counteract the effect. In simple prolongation of the prothrombin time of over 40 seconds, vitamin K_1, 5 to 10 mg. by mouth, is usually sufficient to return the prothrombin time to a safe level without producing complete reversal or resistance to future effect of the anticoagulant preparation. In cases of prolongation of prothrombin time to over 40 seconds, associated with bleeding, 10 to 25 mg. may be given by mouth. In emergencies when there is profuse bleeding or when an emergency operation is contemplated, vitamin K_1 may be given in larger doses of 50 to 100 mg. by the intravenous route as a fat emulsion. By this method bleeding usually ceases in an hour and the prothrombin time is under 20 seconds by three hours. As the intravenous route has been associated, albeit rarely, with toxic effects such as hæmolysis, fever, and histamine-like reactions, the oral route should be used if at all possible and the

intravenous route resorted to only in extreme emergencies. Following large doses of vitamin K_1 the patient is resistant to subsequent use of coumarin anticoagulants for several days. This is presumably due to persistence of vitamin K_1 in the liver for long periods of time.

GENERAL CONSIDERATIONS

The variations of the dose of anticoagulant from patient to patient are related to the sensitivity of the liver system, the rate of turnover of clotting components, the intake of vitamin K_1, and the eccentricities of absorption of the drug from the gastro-intestinal tract. The rapid and complete absorption of warfarin should eliminate the last of these factors, but this still leaves a wide variation of maintenance dose just as there is with dicoumarol and other drugs. Perhaps the variation is less in degree but it is certainly not eliminated.

Following the initial dose of any anticoagulant, there is a rapid disappearance of factor VII from the plasma. This defect prolongs the prothrombin time. As previously mentioned, the three other factors—prothrombin, Stuart factor and Christmas factor—become deficient gradually over the course of five to ten days or more, but this change is not shown in the prothrombin time. This is because factor VII remains the predominant deficiency all the while. As a result of this late and occult change there is more tendency to bleed with prolonged administration of anticoagulants when there is a multi-factor deficiency than with short-term administration. By the same token, however, there appears to be more protection from the hazard of thrombosis when this multi-factor deficiency develops. Consequently, a prolonged prothrombin time, up to 40 seconds in the early phase, is not apt to cause hæmorrhage, and overdose need not be feared. After one week, however, it is advisable to carry the patient in the lower ranges of prothrombin time, and on long-term use the range of 20 to 30 seconds is preferable. This range lessens the danger of hæmorrhage and yet still provides effective coverage against thrombosis in most patients.

A hæmorrhagic state developing rapidly after a small single dose of warfarin was reported by Goodman in one case of cancer of the pancreas and widespread thrombophlebitis. He considers this hyper-reaction as due to over-utilization of clotting factors from intravascular coagulation and consequent rapid depletion of prothrombin. This is an intriguing concept of hyper-reactivity to anticoagulants and he suggests that the response of a patient to a single dose of warfarin might be used as a test for hidden cancer of the body or tail of the pancreas.

As a corollary to the late appearance of a multi-factor deficiency, when immediate effect is desired heparin should be employed. Even though the response of prothrombin time to warfarin intravenously is as fast as to any drug of this type, it is felt in our laboratory that heparin should be continued for the first five days until the period of more definite anticoagulation from multi-factor deficiency appears. This point, however, may be a fine one and is not generally agreed upon. It has been observed that the initial dose of

warfarin and heparin may be given intravenously in the same syringe.

The *indications* for the use of warfarin remain the same as for dicoumarol. Myocardial infarction, particularly of a serious degree, embolism from the heart, phlebitis, pulmonary embolism, and certain forms of stroke have all been shown to be favourably affected by the proper use of anticoagulants.

Contraindications include pre-existing hæmorrhagic disease, liver disease, renal disease with uræmia, ulceration of the gastro-intestinal tract, open wounds with raw surfaces, subacute bacterial endocarditis, recent surgical procedures, particularly of the brain or spinal cord, inlying catheters or drainage tubes, and head injury or stroke with blood in the cerebrospinal fluid. Hypertension is considered to be a contraindication by some observers.

No patient should receive warfarin without daily determination of the prothrombin time. During the first week the prothrombin time should be kept in the vicinity of 25 to 40 seconds. Thereafter a prothrombin time of 20 to 30 seconds is considered adequate most of the time. Periodic observation of hæmatocrit readings, urine, and fæces may disclose hidden bleeding.

Bleeding complications have been reported very infrequently with warfarin: 3 to 10 per cent. of patients. Most of the dicoumarol series show an incidence of bleeding in the region of 15 per cent. The lower rate may be the result of three factors: (a) an ill-defined 'toxic' effect on the capillary wall is less than with dicoumarol; (b) the cases were not treated for so long and therefore did not run into the period where hæmorrhage due to multi-factor deficiency was prone to occur; (c) unpredictable fluctuations of prothrombin time into high ranges could be avoided with warfarin. Until a more factual study of this question appears, it does not seem safe to regard this drug as being significantly less dangerous.

SUMMARY

Warfarin is a highly potent synthetic coumarin which has no toxic effect other than hæmorrhage, is very soluble, may be given intravenously, and is quickly and completely absorbed from the gastro-intestinal tract. An average initial dose of 75 mg. orally or intravenously gives prolongation of the prothrombin time as rapidly as any other coumarin-type of preparation, and maintenance thereafter is achieved with somewhat greater ease than with other preparations. Otherwise its properties, such as anti-vitamin-K effect, delayed effect on coagulation factors other than factor VII, variability of dose from patient to patient, indications and contraindications are the same as with other coumarin-types of anticoagulant.

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MINOR SURGICAL PROCEDURES

VII.—GANGLION

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The term ganglion connotes a cystic swelling arising in relation to tendons and joints of the extremities, and the majority of ganglia are situated about the wrist, hand and fingers. They are rather more common on the dorsal than the ventral aspect of the wrist and are due to myxomatous degeneration in tendon sheath or joint capsule. It is distinctly uncommon to find a ganglion which actually communicates with the synovial cavity of the wrist or carpal joints. In the palm of the hand a ganglion often overlies the proximal end of one of the digital flexor sheaths where it forms a hard, round tumour which may be rather sensitive to pressure. On the back of the fingers ganglia are usually situated at the side of the extensor tendons close to the interphalangeal joints; sometimes they are associated with arthritic changes in those joints. Less common sites of ganglia are the dorsum of the foot and around the elbow, but cystic swellings of identical origin may be seen in relationship to tendons and joints almost anywhere.

INDICATIONS FOR TREATMENT

For all practical purposes the only ganglia which the practitioner is likely to be called on to treat are those about the hand and the dorsum of the foot. A large proportion of these are quite symptomless or cause such slight discomfort that, once the benign nature of the trouble is understood, many patients are readily reassured and do not demand treatment. Spontaneous disappearance of ganglia is quite common so that there should never be any haste in treating them. A few patients with symptomless ganglia are unduly sensitive about their appearance and, even after explanation and reassurance, such people may press for treatment.

Ganglia in the palm of the hand sometimes cause pain and discomfort at work which is sufficient to justify excision. When pain occurs in association with ganglia about the wrist and fingers it is important to be sure that the symptoms are not due to associated arthritis or tenosynovitis. The benign nature of the condition and the tendency to spontaneous cure encourage a policy of non-intervention or, when treatment is indicated, the use of the simplest methods of dispersal.

SUBCUTANEOUS RUPTURE

Eminently simple and satisfactory both for patient and doctor, and entailing little discomfort, the method of subcutaneous rupture by pressure has much to commend it. It is more likely to be successful when the ganglion arises

from superficial structures in an exposed position, as from the extensor tendons at the back of the wrist. The method is generally less practicable for those small ganglia arising on the fingers or in the palmar region. Classically the deed is done with the back of a family Bible or other suitable tome, but it is usually more comfortable and satisfactory if rupture is effected by firm pressure of the operator's thumbs.

Having explained the nature of the procedure to the patient and secured his agreement, the swelling is made more prominent by suitable positioning of the wrist which is rested upon a firm surface. The thumbs are placed close together over the swelling and steadily increasing pressure is exerted. Alternatively, an attempt may be made to break the swelling by a series of short, sharp squeezes. This procedure rarely causes more than mild or moderate discomfort and the quicker it is done the less the patient notices. When rupture of the ganglion has been effected a firm crêpe-bandage support is applied for a day or two. If the operation is unsuccessful a further attempt may be made at a later date or one of the following alternative procedures can be used.

ASPIRATION

The contents of most ganglia are of a somewhat sticky consistency which makes aspiration difficult through a small hypodermic needle. It is wise to use a relatively broad-bore needle of internal diameter about 0.5 mm., and it is much more comfortable for the patient if a small blob of 1 per cent. lignocaine is injected through a fine needle before the aspirating needle is inserted. With strict aseptic precautions, the aspirating needle is pushed through the skin a short distance from the ganglion and not directly over the swelling. A 10-ml. syringe is best to ensure effective suction. Aspiration can sometimes be helped if an assistant presses firmly over the ganglion while the operator keeps both his hands free for steady and effective use of the syringe. In the event of aspiration being unsuccessful it is often possible to disperse the punctured ganglion by firm thumb pressure after withdrawing the needle.

Some have tried injecting irritant solutions, such as iodine or carbolic, after aspirating the contents of the ganglion. Such injections can be exceedingly painful and, in my view, they are *absolutely contraindicated.*

SUBCUTANEOUS INCISION

Short of formal excision this is an alternative treatment which may be tried if rupture and aspiration have failed. Scrupulous asepsis should be observed, the skin being carefully cleaned and, if necessary, shaved. A small weal of 1 per cent. lignocaine is raised about 1 cm. from the edge of the ganglion and the intervening tissues are infiltrated. A fine tenotomy knife (an alternative is a straight sharp cutting-edged needle) is then inserted through the anæsthetized tissues and the wall of the ganglion is incised. After applying

a pad of sterile gauze over the swelling the contents are expelled into the subcutaneous tissues by strong digital pressure.

Following both aspiration and subcutaneous incision a wisp of sterile wool is stuck over the small wound with collodion. A sterile pad is applied over the area and the part is then firmly compressed with a crêpe-bandage support for two or three days. The contents of the ganglion cause no reaction or apparent irritation in the surrounding tissues following either this procedure or subcutaneous rupture by pressure.

OPERATIVE EXCISION

Operation should only be recommended if one or more of these methods have failed and if there is persistent pain and/or disturbance of function. It is prudent to warn the patient that recurrence of the ganglion is possible even after the most careful surgery.

This is most decidedly not 'an office procedure', as our American friends would say, and the operation should only be carried out in hospital. For those who have access to a general practitioner hospital and the necessary basic surgical training, the operation is well within the competence of the good general practitioner. The affected part must be formally and fully prepared according to those standards which normally obtain for operations on tendons and joints. General anæsthesia, exsanguination of the part, properly placed and disposed incision, careful dissection and neat suture of the skin are essential. The technical details, however, are not relevant to this article which is strictly concerned with those procedures which can be carried out in the practitioner's own surgery.

RECURRENCE RATE

After any of these various methods of treatment the recurrence rate is about 25 per cent. over a variable period of time. The fresh swelling is sometimes due to enlargement of a small marginal loculus of myxomatous degeneration. Such a loculus may be left untouched by the simpler methods of treatment and can be similarly overlooked even in the course of excision.

REVISION CORNER

THE CHILD WHO WON'T WALK

FROM the age of ten months, when walking sometimes begins, up to about three-and-a-half years little children cannot be explicit about their symptoms and are often difficult to examine; the diagnosis of the cause of not walking is therefore liable to be puzzling. This brief article is chiefly about

children of this age-group who are able to walk and one day for some reason won't, and those who ought to be walking but for some reason can't.

EXAMINATION

First of all how should such a child be examined so that clinical facts of value will be obtained? If the child is tactlessly handled the chance of making the right diagnosis may be missed and subsequent attempts by the same or another doctor will be still more difficult. If you are seeing the child in a clinic and you wear a white coat take it off: it may have associations for him. You will also do better alone with him and his mother than with a nurse in uniform and other helpers and onlookers present. If you are seeing him at home enter quietly behind the parent and appear as if you had come to mend a gas pipe rather than examine the patient. Don't hurry; imagine you are planning to catch a fish. Learn all you can at first simply by looking, but in so doing avoid looking the child directly in the eyes. Is he intelligent? Is he ill? Is he in pain or afraid of pain? How does he hold himself? Is there any wasting? The eye is as good a judge as the tape measure.

If it is necessary to test for meningism, as in suspected poliomyelitis, leave it to the end. Then, when he is lying quietly, slide a hand under his pillow keeping your other hand on his chest. Raise the pillow and the head together rather quickly and firmly. If the knees jump up Brudzinski's sign is positive. It is far the best test for meningism in a small child, Kernig's sign being difficult to assess at this age, especially if there is pain in the hip or leg. The 'tripod' and 'kiss the knee' signs are useful in cooperative children but the little ones often just won't.

When pain is the cause, the child refuses to put any weight on one leg, and it is usually then possible if sufficient tact is used to locate the painful part by gently manipulating one joint at a time keeping the other still, and comparing it with its fellow in the other leg and by testing for tenderness at the several epiphysial points, beginning at the foot and working up to the hip.

THE CHILD WHO CAN WALK BUT WON'T

(i) *Osteomyelitis.*—Although typically of dramatic onset with fever and constant pain, osteomyelitis quite often presents these days in a less acute form with tenderness only and slight rise of temperature, but the child always looks unwell. X-rays do not help at the onset, nor does a white blood count often. Blood culture should be the next step, when the diagnosis has been made or is strongly suspected clinically.

(ii) *Tuberculous hip or knee.*—Insidious onset. Usually a period of limping before refusing to walk. Eventually considerable spasm of the muscles on manipulation.

(iii) '*The transient hip*'.—This is a retrospective diagnosis and is only a

label that, for want of a better explanation, is applied to those cases in which, associated with or closely following a throat infection, there are temporary pain and limitation of movement of the hip joint and the Mantoux is negative.

(iv) *Slight subperiosteal, epiphysial or articular hæmorrhage* in a child with a bleeding disease may cause refusal to walk, but the signs do not usually remain occult for long.

(v) *Injury.*—It is possible for a child to injure his leg in falling or to wrench it sufficiently to cause pain in a joint or ligament without much to show for it superficially and without the knowledge of his parents. But this is a diagnosis rather to fall back on when the symptoms disappear and no other explanation has been found.

(vi) *Still's disease.*—This diagnosis may be missed by failing to appreciate that, although it usually affects the joints symmetrically (and the knee joints predominantly at this age), one knee may be affected in advance of the other, or the less affected of the two knees may fail to attract notice. It is probably commoner now than tuberculous joints.

(vii) *Poliomyelitis.*—Testing for weakness in a 2-year-old child who is suddenly reluctant to walk is a matter of cooperation or cunning and cannot be described here in detail. The reflexes in the weaker limb are usually diminished early and this is a valuable sign. Occasionally they are very transitorily exaggerated. Muscle pain sets in early in some cases and may suggest the possibility of osteomyelitis or other inflammation but, when the temperature is raised, meningism is rarely absent and this feature usually settles the diagnosis. When the constitutional and meningeal disturbance of poliomyelitis is so mild as to be missed and the child presents only with a weak leg, examination is easier. The reflexes are diminished or absent and wasting is beginning. Vasomotor paralysis causing cyanosis and coldness of the foot should also be looked for.

THE CHILD WHO OUGHT TO BE WALKING BUT CAN'T

(i) *Cerebral palsy* (cases of grosser brain damage excluded).—The early diagnosis of cerebral palsy is important nowadays. In milder cases, for instance the spastic paraplegia that sometimes follows premature birth, the baby is alert, shows his feelings clearly and may have quite good use of his hands. He may want to walk but fail and his parents wonder why. Examination shows a poorer coordination of hand movements than the normal, especially when attempting to pick up a small object such as a bread pill, poorly developed balance of the trunk, and some stiffness of the legs, especially of the adductor muscles. Or there may be an inability to maintain postural tone of the trunk, which sags with a round back, spasticity of the legs being slight or absent, but hair-trigger knee-jerks present. The child usually shows persistence of the infantile startle reflex (Moro reflex)—flinging wide the arms and overbalancing if jolted.

(ii) *Generalized hypotonia.*—The rare 'infantile spinal muscular atrophy'

(*alias* Hoffmann-Werdnig and Oppenheim's diseases) is probably always present from birth although, if mild enough, it is sometimes not appreciated until the stage of walking comes. There is always lateness in acquiring neck control and trunk control. Reflexes are very weak or absent. A generalized softness of muscle tone, without true weakness, for which no explanation can be found, is fairly common and accounts for some children who are merely *late walkers*. Hypotonia is an accompaniment of some *metabolic disorders* (renal acidosis, hypercalcæmia and rickets) and of mental retardation. *Rickets* in England today is practically never due to simple vitamin D deficiency but to renal and metabolic diseases and is now quite rare as a cause of failure to walk. A bad fall, an accident, causing pain but not necessarily any fractures, can send a child into *a state of hypotonia* and even of generalized wasting, which may affect walking for a considerable time.

(iii) *Still's disease beginning under one year.*—Pain in the knees may make a child reluctant to stand or walk and painful wrists and knees may make him reluctant even to crawl. In a plump child the joint effusions or thickening may be missed. A shuffle-bottom method of getting about is all he can manage and his parents wonder why he won't walk.

(iv) *The withdrawn child* (infantile autism, 'psychotic child').—These are children who, though apparently of normal intelligence, fail to make relationships with the outside world or the people in it, but exist on a plane of experience which is that of early infancy, getting pleasure from sensual gratifications only, shut in, unwilling or afraid to make any exploration into the world outside their own person. Such children may be late in walking. More important perhaps is the phenomenon of regression or withdrawal towards this state which may be seen in little children under the shock of separation or loneliness. Serious want of maternal care and affection in the child's own home may produce a similar effect. Such children are immobile. They may rock but they won't walk.

(v) *Raised intracranial pressure.*—The child becomes hypotonic and slightly ataxic and his head circumference is found to be increased by one inch or more above the normal. This slight enlargement may be detected by eye by one who is familiar with children, but will not be missed if measuring the head is made a routine. A circumference of 20 to 21 inches (50 to 52.5 cm.) in a child of 2 is suspicious. The triad of hypotonia, ataxia and enlarged head may begin under one year and be responsible for lateness in walking as well as for a child going off his feet. A posterior fossa tumour is usually the cause. Headache, convulsions and papillœdema are late signs. Vomiting may occur at any stage and is liable to be periodic, falsely suggesting 'tummy upsets' or cyclical vomiting.

(vi) *Hysteria.*—Never make this diagnosis; it will certainly be wrong.

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THE CHILD WHO WON'T TALK

FEW things give parents more pleasurable anticipation than the prospect of their infant learning to speak, and not unnaturally any failure of such development is a cause of grave anxiety. Unfortunately speech has no definite age of development, and many parents worry prematurely; but as a general rule it can be taken that any child over the age of two who cannot say any recognizable words is abnormal.

At first sight the problem of diagnosing the cause of mutism appears formidable, but fortunately the situation is relatively simple provided one remembers that only three things are necessary for speech, and the trouble must lie in one or more of these things. Briefly stated, they are:—

(a) An efficient executive apparatus: e.g., tongue, palate, nasopharynx, cords, respiratory apparatus, including their nerve supply.

(b) A sufficiently developed cerebral cortex to control the executive apparatus.

(c) The ability to hear.

THE EXECUTIVE APPARATUS

This, except the cords, can all be inspected or examined clinically, and in fact troubles here are not a cause of aphasia, but of dysarthria. It is obvious that the child speaks, but pronunciation is poor owing to physical defects. If this is borne in mind it will be seen how monstrous is the operation of cutting the lingual frenum to cure 'tongue tie' in a mute child.

MENTAL DEVELOPMENT

This, the most important factor, has to be considered both as general mental development and as special development of the speech area.

General mental development.—In judging general mental development, progress in directions other than speech has to be assessed, such as the age when the infant first controlled his head (average 3 months); sat up (average 6 to 9 months), crawled (average 9 to 12 months) and walked (average 10 to 24 months). The external stigmata of conditions such as mongolism and cretinism, known to be associated with mental deficiency, must also be recognized. The most important observation of all is an estimate of the over-all behaviour of the child, since, if this is within normal limits for age, the mental development is probably also normal.

Development of the speech area.—Assessment of the speech area is a simple exclusion diagnosis. When the executive apparatus is intact, the general mental development is normal and the child can hear; the trouble is due to delay in development of the speech area and the child has congenital aphasia.

HEARING

In young children this may be very difficult to assess accurately, although

Fisch and Jackson have shown that full audiograms can be done at a much younger age than had hitherto been thought possible. Gross deafness can be shown by lack of response to sudden loud noises but, when deafness is suspected, the opinion of an otorhinolaryngologist is required.

MANAGEMENT AND TREATMENT

Dysarthria.—In some cases, such as cleft palate, surgery can help, but usually the anatomical defects and pathological processes have to be accepted. With the aid of speech therapy a great deal can be done to improve matters.

Mental deficiency.—Except in a few conditions, such as cretinism, nothing can be done to correct the basic trouble. Most cases of mental retardation show some improvement over the years, and the eventual development of speech depends upon the degree to which the mentality develops.

Congenital aphasia.—Fortunately this covers the largest group of cases, and the prognosis in general is excellent. There is a wide variation in the time such children take to become proficient in speech, and before this happens most cases go through the stage of idioglossia, which may cause some confusion. This is an interesting state, but quite simple to recognize because the basic condition is one where vowel sounds can be pronounced, but the consonants are limited. Thus, if the child is asked to repeat the letters of the alphabet it is found most commonly that B, C, D, G, P, T and V are all pronounced the same, as are J, K and X; other consonants may also be affected. The children have a tendency to clip off the ends of many words, and all this makes it very difficult to understand what they are saying. In such cases the parents usually manage to understand their children after a little experience. Speech therapy may sometimes be of help, but as a general rule there is a spontaneous cure and the children learn to speak normally before they are old enough to understand the speech therapist's instructions.

Deafness.—The treatment of deafness is a specialized matter that must be in the hands of an otorhinolaryngologist who, in cooperation with specially trained teachers of deaf children, can effect quite astonishing results.

CONCLUSION

The role of the general practitioner or pædiatrician dealing with a child who won't talk, is essentially that of a diagnostician, and once this has been done the treatment is usually a matter for other people specially trained to carry out this difficult but rewarding task.

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NOTES AND QUERIES

Treatment of Cardiac Dyspnœa

QUERY.—I have a male patient, aged 64 years, who has hypertension, blood pressure 250/140 mm. Hg. The heart rate is regular. In the past an electrocardiogram showed left ventricular strain and myocardial damage due to an old posterior infarction. The blood urea is 47 mg. %, and the x-ray of the chest is normal. He has been on 'myopressin', and 'choledyl', with some benefit, but he still gets severe dyspnœa on waking each morning. I have tried trinitrin under the tongue for this, but there is really no benefit from it. Can you suggest any treatment for the dyspnœa on waking, and any general lines of treatment you may think I have not tried? The patient is a sensible and intelligent person.

REPLY.—The dyspnœa may well be due to incipient left ventricular failure, in the management of which fluid and salt restriction and mersalyl are of value—even in those patients who have no peripheral œdema. If these have not been tried, then they should certainly be given a trial now. Another useful measure which sometimes helps these patients with dyspnœa on waking is to get them to insert an aminophylline suppository into the rectum the last thing at night. SAMUEL ORAM, M.D., F.R.C.P.

Poliomyelitis Vaccination

QUERY.—A baby aged 11 months was given a combined diphtheria-pertussis injection (Glaxo non-mineral) on March 11. Because of a letter from the Health Department advising against combined injections, T.A.F. only was used for the second injection which was given on April 28. An outbreak of poliomyelitis having now occurred and immediate immunization being advised, one wonders what is the best method to adopt. Would it be wise to give the first injection two weeks after the injection of T.A.F. which was given in April and a final T.A.F. two months later, the second poliomyelitis injection being given after a further two weeks? How might the pertussis injection be given?

REPLY.—It is unfortunate that diphtheria prophylactic T.A.F. was selected, as the small amount of horse serum it contains may induce some sensitization. A better antigen for primary immunization of babies is F.T. Perhaps F.T. could be used for the final dose of the course.

As an outbreak of poliomyelitis has occurred, priority is rightly being given to poliomyelitis vaccination. Pertussis immunization is also important, and two further doses should be given this summer. I should be inclined to postpone the final dose of diphtheria prophylactic until all other immunizations have been completed. Intervals of from two to four weeks between injections of different antigens are appropriate in the circumstances, although the possibility of some immunological interference cannot be ruled out entirely when the spacing of doses is short. H. J. PARISH, M.D., F.R.C.P.ED.

First-Aid Kit for the Car

QUERY.—I have decided to carry a small first-aid kit in my car to serve the double purpose of being useful in case of road accidents and as a medicine chest while on camping holidays. I have a small canvas bag, 11 × 11 × 4 inches (28 × 28 × 10 cm.), and would be grateful for advice as to how best to fill it.

REPLY.—For road accidents, dressings and sutures in sterile packs, including a non-adherent dressing ('carbonet'), antiseptic, and morphine and pethidine are sufficient. The morphine and pethidine should be carried in the form of 'ampins'; otherwise a syringe in spirit-proof case and ampoules of sterile water will be needed.

Analgesic tablets, e.g. 'codis'.

Sedatives: amylobarbitone, 0.2-g. tablets, or quinalbarbitone, 0.2-g. tablets.

A broad-spectrum oral antibiotic, e.g. tetracycline, 250-mg. capsules, and pædiatric drops if there are children.

Laxative tablets.

An antihistamine drug, e.g. mepyramine tablets and cream.

A sulphonamide-streptomycin preparation for dysentery, e.g. 'streptotriad' tablets.

Amethocaine 1 per cent. eye-drops.

Tablets for car-sickness (including the dog), hyoscine (1/200 grain [0.3 mg.]) or 'avomine' tablets.

A proprietary anti-fly preparation containing dimethylphthalate.

A thermometer.

Some sunburn lotion.

'Health salts'.

For the medicine chest any favourite remedies for specific known complaints of members of the party should be carried: e.g. for asthma, indigestion and migraine.

What to do in case of drowning should be carefully thought out beforehand, and artificial respiration, preferably by the Holger Nielsen method, should be practised.

Before starting, the reader should be familiar with a book on first aid—such as 'First Aid for the Injured' (St. John Ambulance Association)—to avoid a frenzied search for information when the need arises. For those seeking fuller

details, a book such as 'Emergencies in Medical Practice' (E. & S. Livingstone Ltd.) can be consulted. C. ALLAN BIRCH, M.D., F.R.C.P.

Swimming After Meals

QUERY.—During the summer time, we are frequently warned, and often advocate to children and adults alike, not to enter the water to swim for at least one hour after a meal. May I know the physiological reason for such a recommendation?

REPLY.—For at least an hour after a meal digestion demands the provision of a maximum blood supply to the viscera, with (physiological) peripheral vasoconstriction. Immersion leads to further vasoconstriction in proportion to the temperature of the water; and vascular adjustments may lead to digestive disturbances, naturally influenced by the magnitude of the meal. Other vascular occurrences may be more serious. Coronary arterial constriction occurs: not of great consequence perhaps to healthy young subjects, but potentially dangerous in older, possibly arteriosclerotic, subjects. It is probable that some instances of bathing fatalities attributed to 'cramp' have in fact been instances of cardiac failure. An additional factor is the exertion of swimming, aggravating these vascular disturbances as well as inviting the consequences of hyperventilation.

SIR ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P.

Polycystic Kidneys in Infancy

QUERY.—Last July I delivered a patient, aged 24 years, of her first child. The child died after a normal antenatal and labour record. The cause of death was acute renal failure, the male infant living two hours. Post-mortem examination showed extensive bilateral polycystic disease of the kidneys. Subsequently, I.V.P.s of the parents showed the father to be normal, but the mother showed changes consistent with moderate polycystic disease of both kidneys. She has no clinical or other special signs of this. Her own mother reportedly died when she was aged 40 'due to high blood pressure; and lost three out of nine children in the neonatal period, cause of death not known'.

I would like to know what chances there are of this recurring in the next pregnancy. Can it be expressed as definite 'odds' with the familial pattern mentioned in the textbooks?

REPLY.—The genetics of infantile polycystic kidneys is not completely understood yet. According to the most recent study and review of the literature ('Bilateral Polycystic Disease of the Kidneys', by O. Z. Dalgaard, Copenhagen, 1957) there are two types of infantile polycystic kidneys: (1) Associated with enlarged, spongy kidneys, presumably inherited as a recessive, since familial (but not hereditary) distribution has often been observed. (2) Hypoplastic, cystically converted kidneys, of unknown etiology where the role of genetic factors is not clear and which may possibly not be genetical.

The presence of the adult type of polycystic kidneys in parents of infants with polycystic kidneys is quite unusual. Dalgaard studied intravenous pyelograms of seven parent pairs and found no abnormalities. No other case of hereditary transmission, such as is reported in the case history, has come to my attention. The radiographic diagnosis of polycystic kidneys in the adult is not always simple, and minor normal variation might sometimes be interpreted as polycystic kidneys if the radiographer were especially looking for such a diagnosis. The suggestive family history in the grandmother, however, would be compatible with death due to polycystic kidneys. The chance of recurrence if the child's condition is of the recessive type, (enlarged spongy kidneys) would be 1:4 (apart from the possible complication of similar disease in the mother and grandmother).

Polycystic kidneys in the adult are caused by a dominant autosomal gene with full penetrance by the age of 80 years, i.e. by the age of 80 years, all offspring carrying this gene (on the average 50% of an affected parent) will have polycystic kidneys that can be clinically diagnosed. Patients with the adult type of polycystic kidneys do not have signs and symptoms before the age of 20 years and most will only become clinically affected by middle age.

If the mother has the adult type of polycystic kidneys, the odds will be 1:2 that a child will inherit the gene causing this anomaly but, as stated above, clinical symptoms in a gene carrier cannot be expected until middle age. The probability of the coincidence of both the recessive and the dominant gene in the mother is statistically extremely remote and therefore not likely. In that case, however, the odds remain as stated above for each condition. A possibility to be considered is that the infant's condition represents a developmental malformation occurring against the genetic background of polycystic kidneys and possibly influenced by non-genetic metabolic changes in the mother.

The chance that the infant's condition represents the homozygotic state for a gene that the mother carries must be considered. In order to clarify some of these points and in view of the scientific interest of this case, it would be most desirable to obtain further information of the baby's post-mortem, the grandmother's clinical history and post-mortem, and the mother's intravenous pyelograms. After this

information is obtained a more definite genetic prognosis might be possible for this particular case.

ARNO G. MOTULSKY, M.D.

Keratoplasty in Bilateral Keratoconus

QUERY (from a reader in Iraq).—A patient has bilateral keratoconus. The surgeon advises keratoplasty with a 90% chance of success. What would be the result to the eyes in the event of failure of the operation? The patient has been using contact lenses with great benefit, but complains of pain whenever he uses them.

REPLY.—This is a question to which it is difficult to give a categorical reply, but it is almost certain that the graft would take, though it might not remain clear, in which case the sight would be worse than before. The graft might then be repeated. Keratoconus varies considerably, depending upon how large an area of the cornea is thinned. One can only advise the patient to have one eye grafted as his surgeon recommends.

HAROLD RIDLEY, M.D., F.R.C.S.

Anti-tetanus Immunization

QUERY (from a reader in India).—I should be grateful for advice on the following problem. Nearly 200 adult workers are engaged on this coffee plantation. By the nature of their work they are exposed to sharp cuts, abrasions, and wounds, as they handle sharp tools. These cuts and wounds become soiled and dirty before they can be attended to. None of the workers have been previously actively immunized with tetanus toxoid. The prophylactic treatment with anti-tetanus serum at the time of injury is not free from its own risk.

Would you advise me to undertake a programme of active immunization with tetanus toxoid even for adults, or treat them with serum as a prophylactic measure at the time of injury only?

REPLY.—Active immunization is the method of choice for all workers liable to wounds which may become contaminated with soil, and indeed as a general prophylactic measure for prevention of tetanus. Passive immunization is a poor second choice because it provides less effective and shorter protection and is liable to cause serum reactions and to sensitize to further injections of horse serum. It should only be used for injured patients who have not been actively immunized and should then be followed by active immunization.

LESLIE COLE, M.D., F.R.C.P.

Repair of Vas After Sterilization

QUERY (from a reader in Pakistan).—I have a patient who was sterilized in 1956 by removal of a small length of the vas. As he has recently lost his only son, aged 4 years, he is now anxious to know whether repair is possible. I should be grateful for advice in this case.

REPLY.—It is sometimes possible to carry out a successful end-to-end anastomosis of the vas. I have just had a successful case, and Mr. Reynold Boyd tells me that he has repaired several cases of compulsory sterilization carried out during the Nazi regime. The finest silver or tellurium wire should be used for sutures and the junction should be splinted by threading wire through the lumen at this spot, and bringing this length of wire out through the upper end of the skin around. It is removed on about the fifth day. The technique is similar to that used in the Lespinasse method of carrying out vaso-epididymostomy.

KENNETH WALKER, F.R.C.S.

Testosterone Implantation

QUERY (from a reader in Malaya).—I should be grateful for a detailed description of the technique of testosterone implantation.

REPLY.—Implantation must, of course, be done under full aseptic precautions.

Site of implantation.—I prefer to make the implantation at the upper end of the thigh, about 6 cm. below and behind the anterior superior iliac spine. If the patient habitually sleeps on one side, he is asked to lie on that side.

Local analgesia.—After preparing the skin with cetrimide or a similar antiseptic, a skin weal 1.5 cm. long is raised with 2% procaine or 2% lignocaine (without adrenaline) and the subcutaneous tissue is infiltrated all round to a distance of about 4 cm., using 8 to 10 ml. of analgesic.

Preparation of pellets.—The testosterone pellets are supplied in glass tubes, the outsides of which should previously have been sterilized by soaking in a suitable antiseptic (e.g. 2% carbolic, followed by rinsing in sterile water). The pellets are removed by nicking the tubes with a glass file and breaking on to a sterile towel.

Implantation.—This is most easily done by means of a trocar and cannula, using cylindrical implants. The skin is incised for 0.5 cm., the sharp trocar and cannula is pushed through the incision under, and parallel with, the skin for a distance of 3 cm.; the trocar is then withdrawn, a pellet is inserted into the cannula and is pushed home by means of the blunt obturator. The cannula is withdrawn, reinserted in another direction, and another pellet is introduced. The

process is repeated for each pellet so that, when implanted, the pellets will be more or less equidistant.

If the trocar and cannula is not available, or if lozenge-shaped pellets are preferred, a different technique must be used. The skin incision should be about 1 cm. and, through it, blunt dissecting scissors are introduced so as to open up a pocket under the skin for a distance of 3 cm. Into this the pellet is inserted by means of forceps. Further equidistant pockets are made, one for each pellet.

The skin incision is closed with a single suture of fine silk and a gauze dressing is strapped firmly in place with wide porous adhesive elastic plaster. The patient is instructed to keep the dressing dry, and a week later the stitch is removed.

G. I. M. SWYER, D.M., M.R.C.P.

PRACTICAL NOTES

Differentiating Mitral and Aortic Systolic Murmurs

THE inhalation of amyl nitrite is of value in the differentiation of the apical systolic murmurs of mitral regurgitation and aortic stenosis, according to J. Barlow and J. Shillingford (*British Heart Journal*, April 1958, **20,** 162). During the first fifteen to twenty seconds after the inhalation of amyl nitrite the murmur of mitral regurgitation diminishes in intensity and duration; these changes last for at least twenty seconds and the murmur then returns to its original state. The ejection systolic murmur, on the other hand, remains unchanged (or increases slightly) during the first twenty seconds, and then increases to a maximum intensity twenty-five to forty seconds after the inhalation. The murmur then fades and has usually returned to its original intensity sixty to seventy seconds after inhalation. When the apical systolic murmur is due to a combination of aortic and mitral valve disease, the regurgitation component fades during the first fifteen to twenty seconds, whereas the ejection component increases twenty-five to forty seconds after inhalation of the drug. In cases in which it is suspected that the murmur is arising from both aortic and mitral valves a more accurate interpretation is obtained with two observers—one listening at or inside the apex, and the other outside the apex towards the axilla. The latter will hear the regurgitation murmur fade within the first twenty seconds, whilst the former will hear the ejection component increase between twenty-five and forty seconds.

The Prognosis of Psoriasis

IN a review of 546 cases of psoriasis seen at the Rupert Hallam Department of Dermatology, Sheffield, Ronald Church (*British Journal of Dermatology*, April 1958, **70,** 139) reports that 45.5% were males. The age of onset was predominantly between 5 and 15 years, and it was clear that the earlier the condition developed the more severe and persistent it was likely to become. A family history of psoriasis was obtained from 34% of the patients, and such a history favoured the early development of the disease and increased the probability of its being severe. The total incidence of rheumatoid and psoriatic arthritis was only 2%, which is less than the 3.1% found in the general population. As many as 69% of the patients were unable to suggest any possible reason for the onset of their disease. Infection in the form of an attack of tonsillitis was the commonest precipitating factor and occurred in 7.3%; half of these were under the age of 14 years. Of 260 patients who were treated with tar baths and ultra-violet light, only 4.6% derived no benefit. Over a third were completely cleared of lesions, but in most cases the duration of freedom was only about six months, though some were free for more than five years. Some evidence was obtained to suggest that generalized ultra-violet light once weekly for an indefinite period was beneficial, and the view is expressed that if local authorities set up prophylactic ultra-violet light services 'they would be a boon to psoriatics'.

Prednisone in Purpura

'PREDNISONE, if given in sufficient dosage, is capable of inducing a normal platelet count in most cases of idiopathic thrombocytopenic purpura, whether acute, chronic, or in relapse after previous splenectomy', according to W. Dameshek and his colleagues (*Journal of the American Medical Association*, April 12, 1958, **166,** 1805). In a series of 30 consecutive cases, with this treatment the platelet count rose to normal levels in 22. The initial dosage of prednisone ranged from 20 to 250 mg. daily. When a normal platelet count was achieved, the daily dosage was gradually reduced to 2.5 to 15 mg. In eight cases it was eventually possible to discontinue prednisone therapy completely without a further drop in platelet level and the view is expressed that eventually it will be possible to discontinue prednisone therapy in many of the patients who are in a state of

complete remission on maintenance therapy. Splenectomy was performed in five of the patients who did not respond to prednisone, and in only one of these was there a complete and sustained remission. With one exception, none of the 'usually mentioned serious complications of corticosteroid therapy' were encountered during the two-year period covered by the report, but therapy was discontinued in two instances at the patient's request: one because of 'mild mood disturbance', and the other because she did not like 'her rounded face'. The exception—reported in an addendum—was a 60-year-old woman who did not respond to treatment and who developed osteoporosis and partial compression fractures of three vertebræ in four months of prednisone therapy. It is postulated that the beneficial action of prednisone on the platelet count is due to its producing a reduction in the thrombocytopenic factor.

Iatrogenic Pseudohermaphroditism

Two recent reports illustrate the only recently appreciated risk of inducing masculinization of the female fœtus by administering androgens or progesterone to the mother during pregnancy. A. B. Hayles and R. B. Nolan (*Proceedings of the Staff Meetings of the Mayo Clinic*, April 16, 1958, **33**, 200) give details of two cases in which this effect was produced by progesterone. In the first case the mother had been given intramuscular injections of 10 mg. of progesterone on three successive days during the third month of pregnancy, on account of threatened abortion. In the second case the mother had a history of two miscarriages and was therefore started on the following course of hormone therapy during the first month of pregnancy: November 1953, linguets of progesterone, 10 mg. twice daily; December 1953, 'premarin', 2.5 mg. daily by mouth; March 1954, when there was a threatened abortion, the dose of progesterone was increased to 20 mg. eight-hourly. On June 1 this dose was decreased to 10 mg. four times daily and the administration of 'premarin' was stopped. Progesterone was stopped on June 14 and the child was born on June 27, following a normal labour and delivery.

The second report, by G. Nellhaus (*New England Journal of Medicine*, May 8, 1958, **258**, 935), is of a case of 'nonadrenal female pseudohermaphroditism' in which the mother had been treated with an androgen during pregnancy. Because of a previous miscarriage she was given tablets containing 0.04 mg. of ethinylœstradiol and 10 mg. of methyltestosterone daily for 100 days following the date of her first missed menstrual period. Medication was finally stopped because of deepening of the voice. Details are also given of five previous cases recorded in the literature, in which pseudohermaphroditism occurred in infants born to mothers who had received androgens while pregnant. It is therefore recommended that 'androgenic hormones should be avoided during pregnancy, especially in the third and fourth months, except in the most extreme circumstances'.

Cancer of the Bladder

THE bladder cancers that develop among workers in the dyestuffs industry following exposure to aromatic amines are due to *o*-aminophenols, and do not differ in their natural history or in pathology from the tumours that arise in the general population, according to E. Boyland (*British Medical Bulletin*, May 1958, **14**, 153). Three *o*-aminophenols which are metabolic products of tryptophan, occur in human urine. 'These substances are therefore carcinogens which are products of endogenous metabolism and might be the cause of cancer now considered spontaneous'. They are excreted as conjugates either with sulphuric acid or glucuronic acid, which are hydrolysed by the appropriate enzyme, sulphatase or β-glucuronidase, which is present in the urine. Boyland and his colleagues have shown that both the carcinogenic tryptophan metabolite, 3-hydroxyanthranilic acid, and β-glucuronidase are present in the urine of patients with cancer of the bladder in higher concentration than in normal individuals. The activity of the urinary enzymes can be reduced by oral administration of sodium phosphate, an inhibitor of sulphatase, and of glucosaccharo-1 → 4-lactone, the most potent inhibitor of β-glucuronidase. If 1 g. of saccharo-1 → 4-lactone is taken thrice daily, it reduces the apparent β-glucuronidase activity of the urine by 80 to 90%. A group of patients who have had malignant tumours of the bladder removed are at present under continuous treatment with saccharo-1→4-lactone, in the hope of reducing the chance of development of new tumours. It is also recommended that saccharo-1→4-lactone should be available in factories in which benzidine, 1-naphthylamine and 4-aminodiphenyl are manufactured, so that it could be administered immediately as a prophylactic measure should the worker be contaminated as a result of an accident.

Transmission of Trichinosis

As a result of experiments in guinea-pigs heavily infected with the larvæ of *Trichinella spiralis*, T. E. Gibson (*Annals of Tropical Medicine and Parasitology*, March 1958, **52**, 48) advises that, 'since there is a potential danger that the infec-

tion may be carried on knives, care should be taken by the butcher to clean his instruments between carcases, and the housewife would likewise be well advised to pay particular attention to the cleaning of kitchen utensils used during the preparation of pork before using them to deal with other foods'. The experiment consisted of artificially infecting eight guinea-pigs with *T. spiralis*. After being killed, multiple incisions were made into the thick muscles of the legs with a scalpel or a butcher's knife. Small numbers of larvæ were recovered from the knives or scalpels used on five of the animals. Although never more than 3¾ larvæ were recovered from any one instrument, the view is expressed that 'there is no doubt that as few as two larvæ may produce infection in an animal ingesting them'.

Hazards of Luminous Watches

ON the assumption that the average wrist-watch contains about one-fifth of a microcurie of radium the Medical Research Council estimated that luminous watches and clocks increased the population dose of radiation to the gonads by 1% of the natural background radiation. J. L. Haybittle (*Nature*, May 17, 1958, **181**, 1422), however, has measured the gamma-ray emission from a modern, shock-proof, self-winding watch and found that it contained 2.2 microcuries of radium. Measurements in eight other watches collected from colleagues revealed radium contents ranging from 0.01 to 1.2 microcuries, with a mean of about 0.25 microcurie. He points out that should these watches with a high radium content become popular with the public, 'then luminous watches would be second only to diagnostic radiology in the amount of radiation they contribute to the gonads'. There is the further risk to the skin. His measurements indicate that, on the assumption that a watch containing 2.2 microcuries of radium is worn sixteen hours a day, the skin would receive 0.9 rœntgen a week. This is nearly two-thirds of the present maximum permissible level for exposure to limited parts of the body such as hands and forearms.

Treatment of Snake Bites

IN a review of the incidence of snake bites in the Eastern Mediterranean area, J. L. Turk (*Journal of the Royal Army Medical Corps*, 1958, **104**, 63) states that the classical local treatment is deep incision of the bite and the application of local suction, combined with a tourniquet just above venous pressure, placed round the limb to prevent spread of the venom from the affected limb, and to encourage the collection of œdema fluid to dilute the venom and encourage drainage. He deprecates the use of cauterization and the application of permanganate crystals. In the case of viper bites compression of the limb is scarcely necessary, as the venom is slowly absorbed by the lymphatics: all that is probably required in the way of local treatment is complete immobilization of the limb by the use of sand-bags or a split plaster. A tourniquet should be applied, however, in cases of cobra bite. In the case of viper bites the intravenous administration of an antihistamine drug—e.g. diphenhydramine, 5 mg.,—is effective in cases in which the symptoms resemble those of anaphylactic shock. The aim of treatment in viper bites is to maintain the systolic blood pressure above 100 mm. Hg. Electrolyte imbalance should be corrected. Cortisone has occasionally proved of value. The treatment of cobra bite is the treatment of acute respiratory failure: artificial respiration may prove life-saving. The Institut Pasteur prepares four polyvalent antisera. The recommended treatment is the subcutaneous injection of 10 ml. as soon as possible into the thigh or the neighbourhood of the bite—and repeated as indicated. In exceptional cases, in which the patient's condition is critical, it may be given intravenously.

Fruit Drinks and Dental Erosion

EXPERIMENTS, which 'establish quite clearly that fruit drinks sold in Great Britain cause erosion of rats' and dogs' teeth *in vivo* and of human and dogs' teeth *in vitro*', are reported by P. J. Holloway, May Mellanby and R. J. C. Stewart (*British Dental Journal*, May 6, 1958, **104**, 305). Their experiments included 20 proprietary brands of fruit squashes and cordials, several proprietary brands of cola-type, and other aerated drinks. All the soft drinks tested caused erosion, but this was much less with the cola and other types of aerated drinks than with the fruit-flavoured drinks. The orange juice, as supplied by the Ministry of Health for young children, and bottled blackcurrant juice caused considerable erosion; rose-hip syrup was less destructive. It is considered that the amounts of acid beverages normally drunk by adults are probably too small to be of any great significance, but 'in the young and, especially with certain methods of consumption their influence is without doubt deleterious'. The view is expressed that 'the erosive action of fruit cordials and similar beverages is only likely to become evident, even in children, when large and repeated quantities are taken, and in the usual way this is unlikely, but on the basis of this work, the regular consumption of synthetic or natural fruit juices through the medium of feeding bottles, dummies, in lollipops or even sweets is to be deprecated'.

REVIEWS OF BOOKS

Principles of General Surgical Management. By H. A. F. DUDLEY, F.R.C.S.ED., *et al.* Edinburgh: E. & S. Livingstone Ltd., 1958. Pp. viii and 203. Figures 68. Price 27*s.* 6*d.*

OF the many works dealing with the scientific side of surgery that have come the way of the present reviewer, this is easily the best. Most of them are tinged with the slightly patronizing attitude of the scientist to the clinician, of the whole-timer to the part-timer, of the man who plans methods to the man who treats patients, of the expert in the white coat to the worker in the green overall. This book is written by a working surgeon for his junior colleagues. Mr. Dudley tells in straightforward language that is friendly rather than didactic, all that a young surgeon needs to know; what to do, why to do it, when to do it, and how to do it. Whilst the advice he gives is based upon recent scientific advances, practical 'tips', such as the value of the Kling bandage in retaining a difficult dressing, and the superiority of a plastic tube over the Ryle tube in postoperative gastric suction, betoken the man with bedside experience. The advice given in the text is illustrated from time to time by apposite case histories.

Mr. Dudley has given himself a life sentence. This book will run through many editions, and remain a credit to the great school of clinical surgery that still remembers the name of John Fraser.

Modern Trends in Endocrinology. Edited by H. GARDINER-HILL, M.D., F.R.C.P. London: Butterworth & Co. (Publishers) Ltd., 1958. Pp. ix and 295. Figures 15. Price 65*s.*

THIS book, written by twenty-four contributors who are leading authorities in their particular fields, is a valuable contribution to the literature on endocrinology and gives up-to-date information on many aspects of the subject. The editor states that it has been his responsibility to present a compact volume and he has succeeded, but at the sacrifice of a good deal of material. It is disappointing that he has had to admit that the scope of the work is not intended to be comprehensive: the reason is not given. He is, however, covered by the title: in describing modern trends presumably one need not be comprehensive. The anterior pituitary hormones, the parathyroid glands and infertility in the male are omitted. There is no mention of the recent work on Hashimoto's disease or of nuclear sex in gonadal dysgenesis and Klinefelters' syndrome, and the work of Lawson Wilkins and others on congenital adrenocortical hyperplasia is dismissed in a few lines. On the other hand, the reviewer was pleased to see that one chapter consists of a brief and clear description and analysis of Selye's theory of diseases of adaptation.

Throughout the book a good balance has been maintained between physiology, pharmacology, etiology and treatment, and the subject-matter, as one would expect on seeing the names of the contributors, is well and ably presented. There seems to be only one discrepancy which would confuse the reader: one author states that serious sodium depletion seldom if ever occurs in panhypopituitarism, whereas another affirms that sodium depletion does occur in hypopituitarism with resulting coma and quotes cases of sodium-losing crises in this condition. One minor criticism is the inconsistency in the spelling of the trophic hormones of the anterior pituitary, one or two authors terming them 'tropic': British usage is 'trophic'. The value of the book is enhanced by the bibliography which follows each chapter. The book can be recommended not only to endocrinologists, but to general physicians and those engaged in postgraduate study.

The Biologic Basis of Cancer Management. By FREDDY HOMBURGER, M.D. London: Cassell and Co. Ltd., 1957. Pp. xviii and 354. Figures 10. Price 75*s.*

IN this book the author has tried to review the whole field of cancer from basic research to diagnosis, treatment and preventive medicine. In his foreword Dr. Homburger recommends the book to medical students and physicians and surgeons who wish to keep abreast of the times. Much of the book will contain too detailed and specialized reading matter for them and it is probably more suitable for those already interested in one aspect of cancer and who wish to acquire a wider knowledge. The book is well produced and well arranged. There are many pages of tables in it and it is a little irritating to find these pages not numbered and yet reference made to the page involving counting from the nearest numbered page. In the chapter on experimental carcinogenesis Dr. Homburger states the case impartially and generously pays tribute to Haddow's theory that a concept of cross-linkage offers the best explanation for the same agents being both carcinogenic and carcinolytic. In the chapters on diagnosis of cancer a salutary warning is given of the fallibility of pathologists who have come to be regarded as infallible.

There are three short forewords written by

acknowledged leaders in the cancer field and one cannot do better than quote a sentence from that of Dr. Ackerman of St. Louis who, speaking of Dr. Homburger, says 'He has the remarkable capability of simplifying the problem to an extent that these unrelated disciplines are understandable and the problems that remain to be solved can be seen with better insight'. A good book for all those interested in cancer, with a well-documented list of references arranged for each chapter.

Recent Trends in Chronic Bronchitis. Edited by NEVILLE C. OSWALD M.D. F.R.C.P. London: Lloyd-Luke (Medical Books) Ltd., 1957. Pp. vii and 199. Figures 72. Price 30*s.*

THIS is a first-rate symposium which sharpens the focus on what has been a somewhat woolly subject. After an introduction and an essay on the mortality and morbidity of the disease, Dr. Lynne Reid gives a beautiful exposé of the pathology. The radiological appearances are dealt with by Dr. Simon, and the value of bronchograms is emphasized. Dr. J. R. May has two informative chapters on the bacteriology, and Dr. Oswald examines the troublesome problem of mucus. There are further chapters on air pollution, the disturbances of respiratory function, the cardiological aspects of the disease, clinical management, and aspects of the disease in general practice. The book largely mirrors the experience of the team associated with the chronic bronchitis clinic at the Brompton Hospital. It is pleasurably set out for the reader, and the illustrations are excellent—all in all, a practical monograph, valuable to physicians and also to general practitioners.

Surgery in Infancy and Childhood. By MATTHEW WHITE, M.B., CH.B., F.R.F.P.S., F.R.C.S.ED., and WALLACE M. DENNISON, M.D., F.R.F.P.S.G., F.R.C.S.ED., F.I.C.S. Edinburgh: E. & S. Livingstone Ltd., 1958. Pp. xii and 444. Figures 266. Price 45*s.*

THIS book is intended primarily for the senior medical student and is based upon the authors' experience of supplementing the bedside teaching of such students in the Royal Hospital for Sick Children in Glasgow, with lectures and demonstrations. It may surprise many clinicians south of the border that so much time and care are expended in Scottish medical schools upon instruction in the surgical aspects of the care of children. For the final-year student and even for some postgraduate students, there is an immense amount of information in the 24 chapters. Perhaps there is too much for the treatment of some subjects to be deep enough even for undergraduate students and some might prefer more emphasis upon the iteration of principles than on spreading a fine net so widely for the rare and curious. At a time when there is so much rapid change in surgery, and especially in the midst of the recent surge of advance in pædiatric surgery, it seems a pity that some of the therapeutic revolutions have not been emphasized by the inclusion of more tables and charts comparing the changed results of treatment in the Glasgow Children's Hospital. One might suggest, for example, illustrations of the influence of delay in diagnosis and treatment on mortality, and incidence and complications associated with acute appendicitis, congenital pyloric stenosis or acute intussusception now and in 1938 or 1932. At times emphasis seems misplaced, and it is surprising that the important practical advice on the removal of various foreign bodies from the nose or ear is printed in very small type. An ammoniacal napkin rash is not unknown in breast-fed children. Nevertheless this book should be read by senior students.

Connective Tissue. Edited under the direction of R. E. TUNBRIDGE. Oxford: Blackwell Scientific Publications, 1957. Pp. xii and 371. Illustrated. Price 42*s.*

THIS book consists of the proceedings of the symposium organized by the Council for International Organizations of Medical Science 1956. It should be made clear at the outset, that its subject-matter is highly technical. In the main, the treatment is biochemical, and the majority of the contributions centre upon the source and nature of the 'ground substance' of the soft connective tissues, and the deposition and interrelationships of the various fibres, reticular, collagenous and elastic, that are laid down in this matrix. There are only passing references to the hard connective tissues, cartilage and bone. Within these limits, the monograph is a valuable comprehensive survey of fundamental studies in a field of medical science that has recently been cultivated with vigour and cropped with success. A monograph such as this makes abundantly clear the great potentialities of modern biophysical and biochemical techniques when they can be harnessed together for the investigation of so fundamental a problem as the nature and formation of connective tissue. From biochemical and physiological cytology to pathological cytology is a natural step, and the future applications of these new methods to the study of abnormal tissues may be expected to open up far-reaching advances for the great group of the rheumatic diseases.

Principles of Urology. By MEREDITH F. CAMPBELL, M.D., M.S., F.A.C.S. Philadelphia and London: W. B. Saunders Co., 1957. Pp. xxii and 622. Figures 318. Price 66*s*. 6*d*.

THIS is an excellent introduction to urology by a well-known authority and one particularly well-known in the field of pædiatric urology. The illustrations, both photographic and diagrammatic, are particularly good. By British standards the book is unduly long for an undergraduate, who would not be expected to have such a detailed knowledge of one facet of surgery. At the same time the book is, as the author frankly states, not long enough to form a work of reference. It does, however, give a good over-all introductory view to anyone taking up urology as a special subject. The syllabus of terms in common use given at the beginning must prove helpful in these days when a smattering of the classics no longer forms part of a medical student's general education. For the size of the work there would seem to be an undue amount of space devoted to the subject of enuresis, but this is no doubt the result of the author's pædiatric experience. The series of test questions at the end of the book is a novel and valuable adjunct, as is also the very full bibliography. The book can be recommended cordially to postgraduates taking up urology.

Introduction to Anæsthesia. BY R. D. DRIPPS, M.D., J. E. ECKENHOFF, M.D., and L. D. VANDAM, M.D. Philadelphia and London: W. B. Saunders Co., 1957. Pp. ix and 266. Figures 47. Price 33*s*.

This is a book for the resident anæsthetist and is full of wise advice and excellent practical tips. For example, the chapter on intubation of the trachea is most clearly written, and finishes with the reminder that intubation is rarely an absolute necessity, and that it is not wise to make repeated attempts at intubation. The line drawings are admirably done by Dr. Vandam, but could well have been reproduced far larger than they have been. The book is eminently readable and is well produced, but intentionally contains no discussion of the specialized aspects of anæsthesia such as hypothermia, deliberate hypotension and hypnosis.

Bridging the Gap from Fear to Understanding in Mental Illness. Edited by R. F. TREDGOLD, M.D., D.P.M. London: Christopher Johnson, 1958. Pp. 270. Price 30*s*.

THIS book faces the difficulties of the patient sent to a mental hospital, of his relatives, of the doctors and of the nurses treating him. This approach, written by well-known doctors, two mental-hospital nurses, and with a number of critical letters from ex-patients and patients, is more successful as a composite contribution than could be expected. There is a real effort to combine facts with future needs. There are specific descriptions of mental-hospital problems, the legal arrangements, and the suggestions of the recent Royal Commission. Further, the book is readable. The agencies which the practitioner can approach are outlined, and the whole would be even more welcome if it were nine shillings cheaper. Dr. Tredgold has shown great skill in his mixing of the ingredients. Dr. Bickford, the two nurses, Dr. Cosin and Dr. J. A. Scott are among those who have written sanely, helpfully and interestingly.

Planning for Victory Over Disablement. Edited by NORAH HILL, A.R.R.C. London: Central Council for the Care of Cripples. New York: International Society for the Welfare of Cripples, 1958. Pp. 525. Illustrated. Price 21*s*.

THE author is to be congratulated upon her editing of the Proceedings of the Seventh World Congress of the International Society for the Welfare of Cripples. Many of the articles carry lessons for all clinicians. For those practising physical medicine most of the articles are of interest and especially those dealing with problems of rehabilitation of the disabled. This book demonstrates the lead we in this country have in the services available for the care and welfare of disabled people. It also shows the unfortunate gap in these services: in the provision by local authorities under the National Assistance Act of sheltered workshops for those people too disabled to work in open industry.

The ideas are presented clearly and deserve to be thought about. Bringing together the views of doctors, social workers, physiotherapists, occupational therapists, civil servants and many others concerned with the welfare of the disabled on some problems associated with physical disability, is a service in itself. This mixture acts as a stimulus to further thought. Most important of all is the demonstration once again that we depend one on the other and that without charity there is nothing.

The Story of Heart Disease. By TERENCE EAST, D.M. London: William Dawson & Sons Ltd., 1958. Pp. 148. Plates 11. Price 30*s*.

THIS book comprises the Fitzpatrick Lectures delivered before the Royal College of Physicians

in 1956 and 1957. It is fitting that, in the Harveian tercentenary year, this lectureship, which is devoted to the history of medicine, should have been held by a cardiologist. In the space of four lectures it is not possible to review the whole history of cardiology, but by devoting three to diagnosis, morbid anatomy and therapeutics, and the fourth to the coronary circulation, a surprisingly wide field has been covered, from the very dawn of medicine up to the present day. One of the most attractive features of the book is the inclusion, at length, of quotations from the works of some of the 'old masters' given in their own words. As Dr. East points out, important advances have not infrequently been buried in obscure journals—'Flowers doomed to blush unseen'—and some physicians, like James Hope, have not received as wide recognition as is their due.

The book is attractively produced and illustrated by excellent plates of portraits of some distinguished physicians, and title-pages from their works, many of which come from the author's own collection. It will appeal not only to cardiologists, but to all those interested in the history of medicine.

NEW EDITIONS

A Textbook of Clinical Neurology, by Israel S. Wechsler, M.D., eighth edition (W. B. Saunders Co., 77*s*.).—The first edition of this book appeared over thirty years ago. Although, of course, having the same format as the original, each edition has been meticulously revised and the contents modified to incorporate new knowledge and to reflect fresh attitudes. The present volume contains nearly eight hundred pages and costs thirty shillings more than the previous edition. After the first hundred pages which deal with the principles and methods of examination in clinical neurology, the rest of the book is arranged as a nosological encyclopædia, excellent for reference but tedious for consecutive reading. Each syndrome is accurately described, there is a well-selected bibliography after each chapter, and there is also a good index. A surprising amount of information is crammed into each page.

Practical Electrocardiography, by Henry J. L. Marriott, M.D., in its second edition (Baillière, Tindall & Cox Ltd., 40*s*.) is a great improvement on the first edition. The whole text has been revised and information has been added on the Tp wave, the U wave, systolic and diastolic ventricular overload, parasystole, coronary sinus rhythm and other arrhythmias. The electrocardiogram in angina pectoris does not have a separate section, but is included under coronary insufficiency and elsewhere. The exercise test is mentioned, but little mention is made of the risk in performing this test in patients with coronary disease. Although 'electrocardiographogenic' disease is real and should be prevented by a sound knowledge of electrocardiography, the term used is a most unhappy one.

Histology, by Arthur W. Ham, M.B., F.R.S.C., in its third edition (Pitman Medical Publishing Co. Ltd., 80*s*.), differs from its predecessors by the inclusion of many more electromicrographs all of which are excellently reproduced. A brief account of electron microscopy, radio-autograph and micro-incineration is included. It would appear that this book is the logical outcome of the North American practice of regarding histology as one of the subjects to be studied in the first semester of the medical school. It is needlessly discursive and has been correctly described as the one textbook of histology which one can sit down and read. In the reviewer's opinion histology is best learnt at the microscope. Nevertheless the book has a number of excellent features. Clear, well-illustrated chapters on how histology is studied, a wealth of excellently labelled photomicrographs and related diagrams beautifully reproduced but, whilst the magnification of the electron micrographs is invariably given, that of the photomicrographs is characterized by low power, high power or oil-immersion. Yet this book can by no means be described as a reference book. Pruned of irrelevant material it could well become a worthy addition to the standard textbooks for second- and third-year medical students.

Cleft Palate and Speech, by Muriel E. Morley, M.SC., F.C.S.T., fourth edition (E. and S. Livingstone Ltd., price 27*s*. 6*d*.).—Miss Morley's excellent book is increasing in volume. It is well produced and full of valuable photographs and diagrams. In fact, this is still the best book on the subject to be found on the shelves of English libraries. Perhaps, however, the time has now come for Miss Morley to set about some drastic pruning and to sort and cut out some of the many authorities she quotes. The over-all picture of the palate, its physiology and its repair might then appear in clearer outline in the fifth edition.

The contents of the August issue, which will contain a symposium on 'Industrial Medicine,' will be found on page A 110 at the end of the advertisement section.

Notes and Preparations see page 121
Notes From the Continent see page 125
Fifty Years Ago see page 127
Motoring Notes see page A81
Travel Notes see page A85

NOTES AND PREPARATIONS

NEW PREPARATIONS

'ARTEROCHOL' is 'a pleasantly flavoured emulsion of corn oil combined with vitamin B_6' and is intended for use in lowering the serum cholesterol level in conditions such as coronary heart disease. Each tablespoonful (15 ml.) contains: unsaturated fatty acids in 8.33 g. of corn oil; pyridoxine hydrochloride, 0.6 mg.; and *a*-tocopheryl acetate, 12 mg. Issued in bottles of 12 and 80 fluid ounces. (Ward Casson Ltd., 15 Hay Hill, London, W.1.)

'ATROL' tablets contain 2-dimethylaminoethanol acid tartrate and are intended for those patients needing a mild cerebral stimulant. They are said to have been used with success in cases of schizophrenia and also in patients suffering from periodic headache, functional bowel disorders and chronic fatigue. Issued as 5-mg. tablets in containers of 50 and 500 and as 20-mg. scored tablets in containers of 100 and 500. (Duncan Flockhart & Co. Ltd., 16 Wheatfield Road, Edinburgh 11.)

'NILERGEX' preparations contain isothipendyl and are said to possess 'powerful antihistaminic and anti-allergic properties, coupled with remarkable freedom from side-effects, particularly sedation'. Issued as tablets of 4 mg. for routine use (containers of 50 and 500), coated tablets of 12 mg. for sustained action ('nilergex S.A.'; containers of 20 and 100), and as a 'pleasantly flavoured' syrup containing 2 mg. in each teaspoonful (bottles of 100 and 500 ml.). (Imperial Chemical Industries Ltd., Pharmaceuticals Division, Fulshaw Hall, Wilmslow, Cheshire.)

PHARMACEUTICAL NOTES

PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD. announce two additions to their 'stemetil' range of perchlorperazine preparations:—tablets of 25 mg. of the dimaleate (bottles of 50 and 500), and 2-ml. ampoules of a 1.25% w/v solution of the methanesulphonate (packs of 10 ampoules). (Dagenham, Essex.)

ROBINSON & SON LTD. announce that they are now marketing a disposable face mask which has been specially designed for use in hospitals, clinics and laboratories where it is necessary to prevent the spread of droplet-borne infection and to afford protection from infection. The masks are said to be cool and comfortable to wear, to afford 'adequate protection and coverage with ease of fitting', and may be sterilized. Issued in boxes containing 1 gross and in containers of 24 x 1-gross boxes. (Wheat Bridge Mills, Chesterfield, Derbyshire.)

FILM NEWS

Toxæmia of Pregnancy (16 mm., colour, sound; running time 17 minutes) includes a simple account of the condition and gives advice to the pregnant woman on the way to lead a healthy life during pregnancy. Produced by Dr. and Mrs. W. A. Bullen with the obstetric advice of Dr. Jean Burton-Brown, the film is intended for audiences of expectant mothers and is available on free loan from the Film Library, Pfizer Ltd., Folkestone, Kent.

Cardiac Arrest (16 mm. colour; running time 16 minutes) sets forth a technique for dealing with cardiac arrest by opening the chest wall and massage. Produced by I.C.I. in collaboration with the Postgraduate Medical School of London, it is intended primarily for 'anæsthetists and others who may be faced with a case of arrest in the absence of any surgeon used to thoracotomy', but 'may appropriately be shown to all theatre personnel'. (Film Library, Imperial Chemical Industries Ltd., Imperial Chemical House, Millbank, London, S.W.1.)

MOBILE MEDICAL COLOUR TELEVISION UNIT

THIS unit, the first of its kind to be designed and manufactured in Great Britain, has been manufactured by Marconi's Wireless Telegraph Co. Ltd., for Smith, Kline & French Laboratories Ltd., who intend to place it 'at the free disposal of medical authorities for use at conventions or similar functions'.

B.M.A. PRIZES

THE *Katherine Bishop Harman Prize*, value £75, will be awarded for the best contribution based upon study and research directed to the diminution and avoidance of the risks to health and life that are apt to arise in pregnancy and childbearing. Any registered practitioner in the British Commonwealth and Empire, or the Republic of Ireland, and any member of the B.M.A. wherever resident is eligible to compete.

THE *Occupational Health Prize*, value £50, will be awarded for the best contribution based upon personal observations and experiences in the practice of occupational health. Any member of the B.M.A. who is engaged in the practice of occupational health, either whole-time or part-time, is eligible to compete.

Entries for both these prizes, full details of which may be obtained from the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1, should be submitted not later than January 31, 1959.

EXPERIMENTAL RESEARCH INTO PROBLEMS OF AGEING

THE trustees of the Ciba Foundation announce that not less than five awards, of an average value of £300 each, will be available during 1959 for papers descriptive of research relevant to basic problems of ageing. In making the awards preference will be given to younger workers. Application forms may be obtained from the Director, The Ciba Foundation, 41 Portland Place, London, W.1.

NEW JOURNAL

Cerebral Palsy Bulletin is the title of a new journal, to be published quarterly by the National Spastics Society, 'to stimulate interest in the scientific and clinical aspects of the various forms of cerebral palsy'. The annual subscription is 10s., and the journal is produced by an editorial board consisting of: Professor A. V. Neale, Dr. Ronald Mac Keith, Dr. Paul Polani, Dr. Jack Rubie and Dr. E. Clayton-Jones. (28 Fitzroy Square, London, W.1.)

ARS MEDICA

A COLLECTION of medical prints by great artists of the past, which was presented to the Philadelphia Museum of Art by Smith, Kline & French Laboratories Ltd., will be exhibited as follows during the month of July 1958:—July 1 to 4, at the Gordon Museum, Guy's Hospital; July 10 to 18, Birmingham University; July 21 to 24, St. Helier's Hospital, Carshalton, Surrey, and July 25 to 31, at Charing Cross Hospital Medical School. The collection will be on show at various other centres later in the year, and further information may be obtained from the Public Relations Officer, Smith, Kline & French Laboratories Ltd., Coldharbour Lane, London, S.E.5.

EMPIRE RHEUMATISM COUNCIL

OF the £250,000 for which the Council launched an appeal in January 1957, more than three-quarters was 'still urgently required' at the end of the year, but the twenty-first annual report, for the year 1957, shows that 'definite progress has been made with the ten-year programme of intensified research to conquer arthritis, fibrositis and the many other forms of rheumatism'. Research is carried out under four headings: chemical, physical, psychological, and surveys made by the mobile field unit 'which is the only one of its kind in the world'.

A NEW VOLUNTARY HOSPITAL

THE opening on May 28 of the New Victoria Hospital, Kingston-on-Thames, marks the successful culmination of seven years of intense local effort to provide a hospital in which patients could be treated by the doctors of their own choosing. It was in 1951 that the South West Metropolitan Regional Hospital Board decided to close the local general-practitioner hospital in order to convert it into the gynæcology department of the neighbouring Kingston Hospital. The funds for the new hospital—the first voluntary hospital to be established since the National Health Service Act came into existence—have been largely subscribed locally.

The hospital, which is equipped as a general hospital, has 21 beds. No charge will be made to patients, with the exception of two beds in single rooms for which a charge may be made to private patients.

SCOTTISH EPILEPSY ASSOCIATION

IN the third annual report of the Scottish Epilepsy Association, for 1956-57, it is announced that a workshop to provide sheltered employment for epileptics who may never be able to find employment in open industry, and to train workers so they can later enter into open industry, has been opened in Glasgow. It is intended that the workshop shall become an economic proposition. Two types of work are being done: hosiery linking, and the repair of switchboard cords by sub-contract with the Post Office. The scheme has been approved by the Ministry of Labour for payment of training grants and fees. This enables trainees to approach a degree of production which will ensure some revenue.

NATIONAL VARICOSE FOUNDATION

THE Foundation's future programme includes the building of a new London Varicose Clinic, for which an appeal for £500,000 was launched recently and for which plans have already been prepared. The Foundation is also appealing for more associate members (£1 per annum), and for donations to the research and the lecture and health education funds. (York Road, London, S.W.1.)

SOCIAL SECURITY RECIPROCITY

THE convention on social security between the United Kingdom and Belgium, which came into force on June 1, covers cash benefits provided by the two countries for unemployment, sickness, maternity, old age, widowhood, orphanhood, industrial accidents and diseases, death and family allowances. It enables nationals of either country to add together insurance contributions paid in the two countries, in order to determine the right to receive benefits. Medical benefits under the Belgian health insurance scheme will be available to citizens of the United Kingdom who are employed in Belgium and to

certain other persons who are normally resident there.

A convention on social security, which will come into force when it is ratified, has also been arranged between the United Kingdom and Yugoslavia. This agreement covers the benefits provided by the schemes of national insurance, industrial injuries insurance and family allowances in this country and the corresponding benefits in Yugoslavia. Medical treatment provided under the Yugoslav scheme of health insurance will be available in Yugoslavia to people insured under the United Kingdom national insurance scheme and to their dependants whether working or on holiday there.

PHARMACEUTICAL STERILIZATION BY IRRADIATION

THE use of radiation sources for the sterilization of pharmaceutical preparations is being investigated under the ægis of a working party consisting of scientists from the isotope division of the Atomic Energy Research Establishment, from the School of Pharmacy of the University of London and from eighteen member firms of the Association of British Pharmaceutical Industry. According to the annual report of the Association for 1957-58, the work carried out to date has confirmed the earlier view that the level of radiation required to ensure sterility varies considerably according to the organisms present. The investigations into the effect of radiation on typical pharmaceutical preparations, and substances from which they are prepared, have shown that a certain number of products are adversely affected by a radiation dose of 2.5×10^6 rad, the minimum dose used in the investigation. In other preparations this level of radiation appears to produce no appreciable loss of potency, although some change in colour may occur. The significance of these colour changes is now being investigated.

A PHARMACEUTICAL BICENTENARY

THE Geigy organization celebrates this year the bicentenary of its foundation by John Rudolf Geigy in Basle in 1758. The organization now consists of a network of some 50 companies, operating in over 17 countries. The British section is the second largest unit in the organization. In addition to pharmaceuticals the range of products manufactured by Geigy includes dyestuffs, textiles, chemicals, plasticizers and pesticides.

SOCIAL CLASS AND MENTAL DISEASE

IN 1953, admission rates to mental hospitals for males aged 20 and over for schizophrenia, manic-depressive reaction and psychoneurosis were all highest for patients in occupations assigned to social class V (unskilled labour), according to the recently published 'Supplement on Mental Health' to the 'Registrar General's Statistical Review of England and Wales for the years 1952-1955'. For disorders of behaviour, character and intelligence, classes I (professional) and V had rates considerably higher than the other classes. Estimated first admissions for schizophrenia increased from 88 per million population in class I to 383 in class V. For manic-depressive reaction, rates were 235 in class I and 213 in class II, increasing to 392 in class V. For alcoholism, rates in class I were considerably higher at ages 35 and over than for younger men. In class V there was not the same marked difference in rates between the age-groups.

AIRPORT SANITATION

THE number of air travellers in scheduled flights throughout the world is expected to surpass the 100 million mark this year. This tremendous increase may soon overtax the facilities at many international airports, according to the WHO expert committee on sanitation of international airports, which met recently in London under the chairmanship of Sir Harold Whittingham, the former medical director of B.O.A.C. One of the interesting points brought out at this meeting was the potential danger of rats. Only very rarely do they get on board aircraft, but if they do, they can gnaw through aluminium and plastic tubing in their search for food and water, and they have been known to gnaw through wires in aircraft.

SMALLPOX IN PAKISTAN

THE current smugness over the grossly undervaccinated state of the country is disturbingly belied by the latest news of the epidemic of smallpox which is now sweeping over Pakistan. Preliminary figures received so far this year indicate that there have been more than 35,000 cases, with more than 15,800 deaths. Now that air travel has brought Britain so uncomfortably close temporally to outbreaks such as this, it is clear that the Ministry of Health should be given every possible support by the practitioners of the country in their attempts to persuade parents to allow their children to be vaccinated and so saved from the dire consequences of this killing and mutilating disease.

SMOKING AND CARIES

'FROM observation it would appear to be a fact that smoking increases resistance to caries',

according to C. R. Peers (*Brit. dent. J.*, 1958, **104**, 348). Apparently the Indians of Panama use the residue from their tobacco pipes as a preventive against dental decay, and it is suggested that this matter might be worth further investigation.

PUBLICATIONS

The Physiology of Learning, by W. Ritchie Russell, C.B.E., M.D., F.R.C.P., is the 1957 Morison Lecture of the Royal College of Physicians of Edinburgh. It is a stimulating—if, at times, provocative—epitome of the implications of recent trends in neurophysiology for parents, educationalists and doctors. The author is to be congratulated on a brilliant piece of synoptic writing which will appeal to all discriminating practitioners. (Royal College of Physicians of Edinburgh, price 3*s.* 6*d.*)

Modern Drug Treatment in Tuberculosis, by J. D. Ross, M.B., CH.B., F.R.C.P.ED., represents an excellent summary of the modern treatment of tuberculosis. It is well written and conveniently arranged in sections with concise explanations of the problem of drug resistance and the nature of sensitivity tests, which comprise such an essential preliminary to treatment. It is a thoroughly readable and practical book containing much valuable information and should meet a much needed demand for those in general practice and for hospital residents. (National Association for the Prevention of Tuberculosis, price 5*s.*)

Stuttering: A Psychodynamic Approach to its Understanding and Treatment, by Dominick A. Barbara, M.D., F.A.P.A., begins with a well-documented account of the facts and theories relating to stammering. The author, himself a cured stammerer, then describes the psychotherapeutic methods which he employs. These are based upon the advanced analytical teachings of the late Karen Horney, and emphasize the patient's idea of himself and how it can be changed. The various psychological problems peculiar to stammering are fully discussed. This book is invaluable for psychiatrists and others who cooperate with speech clinics, as well as for speech therapists themselves. It supplements the commoner type of publication which limits itself to a description of practical methods employed for the freeing of speech. (Hutchinson Medical Publications, price 25*s.*)

The Doctor as a Person, by Harold Dodd, CH.M., F.R.C.S., is an evaluation of the work and duties of the doctor in terms of the Christian ethos. (The Tyndale Press, price 6*d.*)

Intermediate Hosts of Schistosoma (WHO Monograph Series, No. 37), by G. Mandahl-Barth, represents an attempt on the part of the World Health Organization to clarify the nomenclature of those snails which serve as intermediate hosts for schistosomiasis. As this branch of knowledge —malacology—has grown it has become more complicated, and original descriptions of the species have often been found to be too brief to enable them to be differentiated adequately. The field is too large for one man to tackle but Dr. Mandahl-Barth is to be complimented on the effort he has made. In the preface it is noted that the conclusions presented have been critically reviewed by several malacologists but that no general agreement has been reached. (H.M. Stationery Office, price 20*s.*)

Diabetes is a series of questions and answers prepared 'in an attempt to answer some questions about diabetes which are commonly met'. (Research Defence Society, 11 Chandos Street, London, W.1, price 6*d.*)

The Hangover, by Benjamin Karpman, M.D.— The author of this book attempts a new approach to the understanding of the psychodynamics of alcoholism through the medium of the physical and emotional effects of the so-called 'hangover', which he graphically describes as 'a slice of life in the lives of alcoholics'. There is a well-written but tediously long description of the drinking histories of seven male and seven female alcoholics. At the end of each autobiography, Dr. Karpman offers an interpretation, which in the main is no interpretation at all, but merely a summary of the various events in the alcoholic drama. Because of its somewhat novel approach, this book might possibly interest those specializing in this particular field, but we cannot recommend it to our readers. (Blackwell Scientific Publications, price 72*s.*)

OFFICIAL PUBLICATION

Report of the Central Health Services Council for the Year ended December 31st, 1957, reviews the reports published by the Council's standing advisory committees during the year. The subjects dealt with include welfare foods, control of dangerous drugs and poisons in hospitals, poliomyelitis vaccination, industrial occupation schemes in mental and mental deficiency hospitals, the training of clinical psychologists, and tuberculosis among immigrants. The views expressed on this last subject will cause concern to many of those who are responsible for the protection of the health of the citizens of the United Kingdom. (H.M. Stationery Office, price 1*s.* 6*d.*)

NOTES FROM THE CONTINENT

A European Newsletter

BELGIUM

Nephropexy.—The only indication for nephropexy, according to P. Derycke, is nephroptosis resulting in interference with urinary excretion to such an extent as to cause dilatation of the ureter. He considers neither of the two commonly used methods of fixation satisfactory: i.e. fixation by means of the capsule, or through-and-through fixation of the renal parenchyma, the suture being tied round one of the lower ribs. As an alternative he recommends suspending the kidney from the 11th or 12th rib by means of kangaroo tendon fastened to the renal capsule with fine nylon thread. The kangaroo tendon is said to be absorbed slowly without any risk of infection or irritation of the tissues. The results have been excellent in all of the 40 cases in which he has used this new method.

Nalorphine.—The value of nalorphine in the treatment of respiratory depression due to opiates is well exemplified by a case reported by A. Deleixhe and J. Lecomte, of Liège. The patient was a lad of 17 who was found unconscious one morning at 09.00 hours. It subsequently transpired that he had attempted suicide by swallowing 100 mg. of a preparation known as 'acedicon', the active constituent of which is acetyl-dimethyl-dihydrothebaine. When first seen he was deeply cyanosed and the respiratory rate was only 4 to 6 a minute. An emergency tracheotomy was performed, followed by the slow intravenous infusion of methylamphetamine hydrochloride (150 mg. per litre) and aminophylline (500 mg. per litre), but with little improvement in the patient's condition.

At 11.00 hours, an intravenous injection of 10 mg. of nalorphine was given. This was followed by an immediate improvement: the respiratory rate rose to 16 a minute, the cyanosis disappeared, the pulse rate, which had been running around 150 a minute, fell to within normal limits, the reflexes became more active, and the pupils dilated. From this time onward the boy's condition remained satisfactory, but he did not recover consciousness until the sixth day.

Calcium disodium versenate in hæmochromatosis.—The effect of calcium disodium versenate in two cases of hæmochromatosis was discussed by R. Crismer and his colleagues at a meeting of the Belgian Society of Gastro-enterology. The course of treatment was 1 gramme intravenously each day for five or six days. This was repeated after a break of five to six days. Each course of treatment was followed by an increase in the excretion of iron in the urine, but this only persisted during the time the drug was being given. The amount of iron excreted reached a total of 1 gramme, which was less than that excreted following treatment by means of bleeding. The level of the serum iron fell during treatment—only to rise again subsequently. This rise is attributed to mobilization of the iron reserves. Although there was thus no evidence that this form of treatment was any more effective than bleeding, there was no evidence of toxic effects and the drug was well tolerated by the patients.

Poliomyelitis vaccination.—Plans have now been completed for the poliomyelitis vaccination programme this year. The vaccine is being bought by the Ministry of Health and distributed free to local authorities, who are responsible for planning the actual vaccinations. Priority is to be given to children between the ages of six months and six years.

FRANCE

Constrictive pericarditis.—The value of catheterization of the heart in the diagnosis of atypical cases of constrictive pericarditis, particularly in deciding whether or not surgical intervention is indicated, is stressed by P. Soulié and his colleagues. Their report is based upon a series of 50 cases. The conclusion reached is that there is seldom any difficulty in picking out these atypical cases and deciding in which surgical intervention is indicated provided all the symptoms and signs are carefully considered, and cardiac catheterization is carried out should the diagnosis still be in doubt.

Tricuspid incompetence.—On the basis of their findings in 111 cases, the clinical features of tricuspid incompetence are summarized as follows by J. Himbert and his colleagues. On auscultation there was a systolic murmur at the lower end of the sternum, and in 25% of cases this murmur was either accentuated, or was only heard, at the end of inspiration (Carvallo's sign). Radiologically the heart was enlarged in all cases, with enlargement to the right and rounding of the apex in half the cases, whilst at the same time the lung fields were clear. The electrocardiographic features were atrial fibrillation in

66% of cases, with evidence of right atrial hypertrophy and hypertrophy of either the right ventricle or both ventricles.

The liver was enlarged, pulsating and painful in 95% of cases, and there was congestion of the veins of the neck in practically one-quarter of the cases. The mean venous pressure was 21 cm. of water. Œdema was present in 68% of cases, and ascites in 25%. Shortness of breath was present in 80% of cases, but was of differing origin: e.g. chronic bronchitis, pulmonary congestion, pulmonary embolism. The average age at death of the 40 patients who died during the period of observation was 38.8 years: more than half of them were between the ages of 24 and 46. Just over half of them died within less than six months of first coming under observation.

'Collagenosis'.—A new concept and classification of the so-called 'collagen diseases' is proposed by Jean de Brux, on the basis of more recent data on the action of alpha- and gamma- globulins. This classification is as follows:—

(i) Acute, and often transitory, conditions, characterized initially by thrombosis and exudate, followed by an increase in alpha- and gamma-globulins and a cellular reaction. This group includes serum sickness.

(ii) Subacute and chronic conditions:

(a) With minimal tissue necrosis and a secondary cellular reaction. Initially there is a marked increase of $alpha_2$-globulins, followed by a slow change to gamma-globulins. This subgroup includes acute rheumatism, dermatomyositis, and temporal arteritis.

(b) With marked tissue necrosis, followed by leucotaxis and then a 'lympho-plasmocytic' reaction. There is a marked increase of $alpha_2$-globulins. This subgroup includes polyarteritis nodosa.

(c) With massive tissue necrosis, but no secondary cellular reaction. Here there is a marked increase of gamma-globulins. This subgroup includes disseminated lupus erythematosis, generalized scleroderma with renal involvement, and possibly some forms of amyloidosis.

Chronic mediastinitis.—Chronic mediastinitis, according to M. Bariéty and his colleagues, is a diagnosis which has waxed and waned in popularity in France, but they suggest that the newer methods of investigating the mediastinum justify a fresh review of the subject. In a series of 240 cases of infection of the mediastinum they found seven cases of diffuse chronic mediastinitis. The condition is practically always secondary to involvement of some neighbouring structure such as lymph nodes, the lungs or pleura, the œsophagus or the vertebrae. In diagnosis, stress is laid upon the importance of radiological investigation, including angiography and mediastinography, and œsophagoscopy. Treatment is dependent primarily upon the underlying cause: e.g. anti-tuberculous, anti-syphilitic, or irradiation (or chemotherapy) in the case of malignant disease. A certain number of cases are associated with the superior vena cava syndrome, and in them excellent results are being obtained from surgical treatment of the syndrome.

Pneumoconiosis.—E. Balgairies has recently reviewed the present status of the non-sclerosing pneumoconioses. These have a characteristic radiological picture: dense, pinhead, rounded shadows. Clinically they are characterized by the rarity of superadded tuberculous infection, and a sputum containing large amounts of the causative metal. This group of pneumoconioses includes siderosis, barytosis, stannosis and 'zincosis', but not the pneumoconiosis of coal-miners.

With his colleagues in the coalfields of the Nord and the Pas-de-Calais, he has drawn attention to the fact that in more than 20% of cases the tumour-like shadows in films of the lungs of coal-miners with pneumoconiosis are due, not to localized areas of fibrosis, but to localized collections of fluid. They can often be seen to have a fluid level and may manifest themselves clinically by the expectoration of sputum which is as black as Chinese ink. In some cases, however, they can only be detected by means of transthoracic puncture. The fact that they are constantly sterile indicates that they are not tuberculous in origin. It is suggested that they may represent an allergic reaction due to the tissues becoming sensitized to proteins denatured by the toxic action of the coal dust.

Hepatic coma during pregnancy.—P. Houel and his colleagues have analysed a series of 22 fatal cases of hepatic coma, due to acute viral hepatitis, occurring during pregnancy. They were all multiparæ and the hepatitis developed at the beginning of the third trimester. The fatal course of the disease is attributed to metabolic and endocrine disturbances associated with the stage of pregnancy at which the original viral infection was acquired. Rapid death of the fœtus *in utero* occurred in 18 cases, and spontaneous delivery occurred in 15 cases. The authors do not recommend induction of labour in such cases. They found no form of treatment of any avail.

'Notes from the Continent' are produced in collaboration with the Editors of Bruxelles-Médical (*Belgium*), La Revue du Praticien (*France*), Münchener Medizinische Wochenschrift (*Germany*) and Minerva Medica (*Italy*).

THE PRACTITIONER

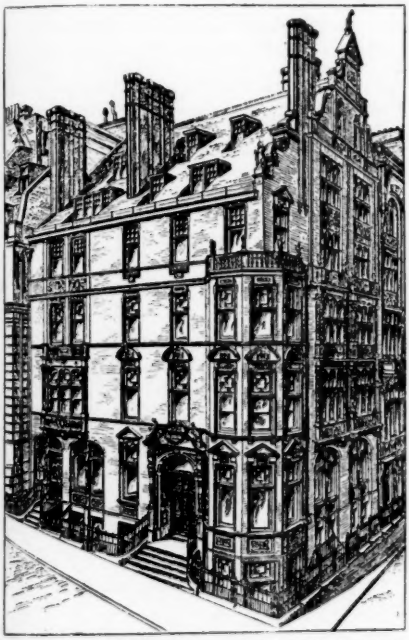
Fifty Years Ago

'Truth is a glorious thing and an enduring thing, but it seems no easy matter to convince men of it'.

—Plato: *Laws* Book ii.

JULY, 1908

'NOTES by the Way', reduced to a modest page, announce with regret that 'We have not yet been able to take possession of our new building as, unfortunately, several unforeseen circumstances have arisen which have caused delay and hindered the workmen'. An illustration of the



The offices of *The Practitioner*, in Howard Street, off The Strand (1908-1928).

building faces page 1. This Victorian building still stands today and was occupied by *The Practitioner* until 1928.

The entire number is devoted to 'Health Resorts and Climatic Treatment' and has been edited by Neville Wood, M.D., M.R.C.P., whose 'wide climatological experience has materially contributed to the success of the work'. 'Notes and Comments' from the Editorial pen begin with reflections entitled 'Credulity and Mockery': 'Balneology has, throughout its history, been the subject of conflict between the somewhat excessive faith of its local believers and undue scoffing from outside. Both parties to the dispute have claims upon our sympathy. It devolves upon the man at the Spa to use waters which defy exact analysis, and whose physiological action cannot be stated with precision. Unless he is sufficiently enthusiastic regarding these waters, his place of usefulness is not at a Spa. He will forfeit the confidence of his patients and so lose all control over their actions. They would resent, moreover, any little clinical lectures, with nicely balanced expressions of scientific doubt, in the manner accounted orthodox by the junior assistant physician. In his environment he must use the potent therapeutic factor of suggestion. About this, however, there is a magic under the spell of which the suggester is himself apt to fall. He thus becomes imbued with that credulity which . . . has provoked remonstrance from outside'. The Editor goes on to explain that 'Locally written descriptions have been largely requisitioned, and local opinion has been considered by all the other authors, as well as by its Editor, who is responsible for the unsigned notices . . . The omission of a separate paper on the French Riviera is due to its proposed author having at the last moment been attacked by influenza, a scourge which seems lately to have acquired a special virulence in that sunny region'.

The opening article 'On Climates Suitable for the Aged' is contributed by Sir Hermann Weber, M.D., F.R.C.P.: 'Egypt offers abundance of sunshine and warmth with only rare rainy days. Even the most aged person can spend almost the whole day in the open air. The mind is cheered not only by the sun and the beautiful sunrises and sunsets, but is also agreeably occupied by the remains of the oldest civilisation and art, and is amused by the habits and life of the Arabs, and of the visitors from many countries'.

J. Walter Carr, M.D., F.R.C.P., Senior Physician to the Victoria Hospital for Children, Chelsea, describes 'Health Resorts and Climates for Children'. F. Parkes Weber, M.D., F.R.C.P., Physician to the German Hospital, London, writing on 'Change of Air in Young Adult Life and Early Middle Age', emphasizes that 'Even with so simple a method of treatment as "change of air" and open-air exercise, there may be dangers. How often has not a chlorotic young woman been taken by her kind friends for an ordinary holiday in the country, and with more or less unsatisfactory results! Chlorosis is as

frequent in many parts of the country as it is in London and other large towns, or even more frequent . . . It is almost as important to separate chlorotics from the class for which a mere holiday in the country can be recommended as it is to distinguish early cases of pulmonary tuberculosis'.

James Mackenzie, M.D., deals with 'Spa Treatment of Affections of the Heart': 'Another factor that helps greatly in treatment is a quiet and contented mind . . . When an elaborate system of cure is carried out without fatigue . . . the patient's mind is occupied, and the pomp and circumstance with which the "cure" is carried out, go a great way to comfort the mind, and brighten it with hope as to the issue of the treatment'. P. Horton-Smith-Hartley, M.V.O., M.D., F.R.C.P., F.R.Met.Soc., Physician to the Brompton Hospital, contributes a short summary 'The Configuration, Metereology, and General Health of the Midland Counties of England'.

The titles of the remaining articles read almost like a Cook's conducted tour to enticingly romantic places: 'The Portuguese Riviera', 'Gibraltar, Algeciras, Ronda', 'The Italian and Swiss Lakes', 'Health with Pleasure in Norway', 'Vichy', 'Aix-Les-Bains', 'Wiesbaden', 'Baden-Baden', 'Marienbad', 'The West Indies', 'The Canaries', 'Voyages to the East', 'Egypt and North Africa', 'Health and Travel in South Africa'.

'There are no "health resorts" in Canada which may be well compared with those in older communities', begins an article on 'Health Resorts in Canada' by Andrew Macphail, M.D., McGill University, Montreal. 'Life is not sufficiently organized, and Canadians do not fully appreciate the luxury of a leisurely convalescence. There is not yet a class of idle rich who require to divert themselves from their amusements by a period of illness'. This delightful essay concludes: 'But much more important to the seeker after health than formal resorts are the devices which Canadians themselves employ . . . Life in the woods is extremely simple, and it is a sovereign remedy for disturbance of the digestive and nervous systems. Canadians are a kindly people, and any visitor with some slight introduction can easily gain admission to these silent places'. Pathologist, educator, medical historian, editor, and writer, Andrew Macphail graduated M.D. at McGill in 1891 and in 1907 became professor of medical history in the University. He was knighted in 1918 for his war services. His literary career began as reporter to the *Montreal Gazette*. For many years he edited the *Canadian Medical Association Journal*. As Editor of the *University Magazine* he made this quarterly the leading intellectual review in Canada. Essayist, novelist, anthologist, and biographer of Thomas McCrae, he possessed a pungent, provocative, and epigrammatic style and said the drollest things with the most melancholy expression.

W. R. B.

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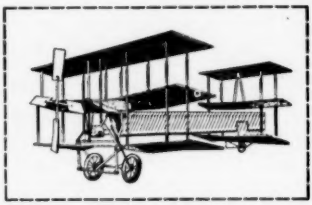

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